MCR 2018

HEINRICH HEINE
UNIVERSITÄT DÜSSELDORF

MCR 2018

7th International Conference on Multicomponent Reactions and Related Chemistry

August 26th to 31st, 2018

Heinrich-Heine-Universität Düsseldorf
Germany

Content

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Dr. Jost Henkel Stiftung
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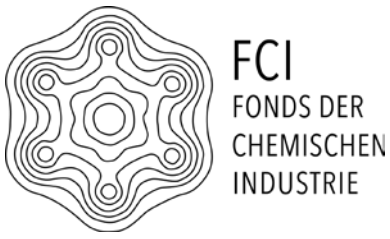
Advion



Welcome

Dear participants,

As the chairman of the "7th International Conference on Multicomponent Reactions and Related Chemistry" and on behalf of International Advisory Board, I am delighted to welcome all of you to Düsseldorf for this very exciting scientific program in multicomponent chemistry.

This conference continues the series of six previous highly successful conferences on the same topic that were held in Munich (2000), in Genova (2003), in Amsterdam (2006), in Ekaterinburg (2009), in Hangzhou (2011), and in Brasilia (2015). The academic program of this conference encompasses 6 plenary lectures, 23 invited lectures, 31 oral and more than 50 poster presentations aligned in the thematic fields of synthetic methodology (multicomponent, cascade, and domino reactions and one-pot processes), conceptual approaches in diversity-oriented synthesis and applications in medicinal, heterocyclic, and natural product chemistry. With this, the conference indeed covers all exciting aspects in modern one-pot synthetic chemistry.

The conference venue on the campus of Heinrich Heine University (HHU), a young university that just celebrated its 50th anniversary, insures a stimulating academic atmosphere for exchange and discussion between speakers, presenters and the audience.

Apart from the scientific program the city of Düsseldorf, the state capital and political and economic center of the federal state Northrhine-Westfalia with 600.000 inhabitants, promises a rich cultural program from music, opera, classical and contemporary art to modern architecture and many opportunities to enjoy life in the "Altstadt", the old city, with numerous bars, breweries, restaurants and cafés, also on the Rhine promenade.

The chairman and the local organizing committee, would like to thank all the conference sponsors, the International Advisory Board, all speakers, poster

presenters and most of all, the participants, which will ensure that MCR 2018 will be an exciting, rewarding, memorable and sparkling symposium, setting the stage for future MCR conferences.

Chairman of MCR 2018
Prof. Dr. Thomas J. J. Müller, HHU Düsseldorf, Germany

Local Organizing Committee

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(HHU Düsseldorf, Germany)

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(HHU Düsseldorf, Germany)

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(Zhejiang University, China)

Prof. Carlos Kleber Zago de Andrade
(University of Brasilia, Brazil)

Prof. Andrei K. Yudin
(University of Toronto, Canada)

Schedule

Sunday, August 26	
16:00 20:00 h	Registration and welcome reception

Monday, August 27	
08:00-08:30 h	Registration
08:30-09:00 h	Official Opening
	Chair: Thomas J. J. Müller
09:00-09:50 h	Chao-Jun Li, McGill University, Montreal, Canada (PL-01)
09:50-10:20 h	Alexander Dömling, University of Groningen, Netherlands (IL-01)
10:20-10:50 h	Luca Banfi, Università degli Studi di Genova, Italy (IL-02)
10:50-11:20 h	Coffee break
	Chair: Yangung Wang
11:20-11:50 h	Rodolfo Lavilla Grifols, Universitat de Barcelona, Spain (IL-03)
11:50-12:05 h	Shabnam Shaabani (SL-01)
12:05-12:20 h	Jordy M. Saya (SL-02)
12:20-13:30 h	Lunch break
	Chair: Leonid G. Voskressensky
13:30-14:00 h	Thierry Constantieux, University of Aix-Marseille, France (IL-04)
14:00-14:30 h	Daniel G. Rivera, University of Havana, Cuba (IL-05)
14:30-14:45 h	Ouldouz Ghashghaei (SL-03)
14:45-15:00 h	Eduardo González-Zamora (SL-04)
15:00-15:30 h	Coffee break
	Chair: Daniel G. Rivera
15:30-16:00 h	Valentin A. Chebanov, National Academy of Sciences of Ukraine, Charkiv, Ukraine (IL-06)
16:00-16:15 h	Ana Mallo-Abreu (SL-05)
16:15-16:30	Saeed Balalaie (SL-06)
16:30-16:45 h	Ping Lyu (SL-07)
16:45-17:00 h	Alexey A. Festa (SL-08)

Tuesday, August 28	
	Chair: Erik Van der Eycken
09:00-09:50 h	Jared T. Shaw, University of California, Davis, USA (PL-02, Dr.-Jost-Henkel Lecture)
09:50-10:20 h	Carsten Schmeck, Bayer Pharma Wuppertal, Germany (IL-07)
10:20-10:50 h	Andrei K. Yudin, University of Toronto, Canada (IL-08)
10:50-11:20 h	Coffee break
	Chair: Mikhail Krasavin
11:20-11:50 h	Géraldine Masson, Institut de Chimie des Substances Naturelles, Gif-sur-Yvette, France (IL-09)
11:50-12:05 h	Constantinos G. Neochoritis (SL-09)
12:05-12:20 h	Tetyana L. Pavlovska (SL-10)
12:20-13:30 h	Lunch break
	Chair: Constantin Czekelius
13:30-14:00 h	Lars Bärfacker, Bayer Pharma Wuppertal, Germany (IL-10)
14:00-14:30 h	Mikhail Krasavin, St. Petersburg State University, Russian Federation (IL-11)
14:30-14:45 h	Maryna V. Murlykina (SL-11)
14:45-15:00 h	Bernhard Westermann (SL-12)
15:00-15:30 h	Coffee break
	Chair: Andrei K. Yudin
15:30-16:00 h	Laurent ElKaim, ENSTA ParisTech, Palaiseau, France (IL-12)
16:00-16:30 h	Carlos Kleber Zago de Andrade, Universidade de Brasília, Brazil (IL 13)
16:30-16:45 h	Markella Konstantinidou (SL-13)
16:45-17:00 h	Syeda Aaliya Shehzadi (SL-14)
	Chair: Klaus Schaper
17:00-20:00 h	Poster session

Wednesday, August 29	
	Chair: Alex Dömling
09:00-09:50 h	Magnus Rueping, RWTH Aachen, Germany, and KAUST Catalysis Center, Saudi-Arabia (PL-03)
09:50-10:20 h	Romano V. A. Orru, Vrije Universiteit Amsterdam, Netherlands (IL-14)
10:20-10:50 h	Maxim A. Mironov, Ural State University, Ekaterinburg, Russian Federation (IL-15)
10:50-11:20 h	Coffee break
	Chair: Romano V. A. Orru
11:20-11:50 h	Hans Ulrich Reißig, Freie Universität Berlin, Germany (IL-16)
11:50-12:05 h	Cecilia Ines Attorresi (SL-15)
12:05-12:20 h	Pieter Mampuys (SL-16)
12:20-13:30 h	Lunch break
	Chair: Laurent El Kaim
13:30-14:00 h	Leonid G. Voskressensky, Peoples' Friendship University of Russia, Moscow, Russian Federation (IL-17)
14:00-14:30 h	Georg Manolikakes, TU Kaiserslautern, Germany (IL-18, JCF Lecture)
14:30-14:45 h	Alissa C. Götzinger (SL-17)
14:45-15:00 h	Renata Riva (SL-18)
15:00-15:15 h	Heiner Eckert (SL-19)
15:15-15:45 h	Coffee break
	Chair: Carlos Kleber Zago de Andrade
15:45-16:15 h	Valentine G. Nenajdenko, Lomonosow Moscow State University, Russian Federation (IL-19)
16:15-16:45 h	Harald Gröger, University of Bielefeld, Germany (IL-20)
16:45-17:00 h	Francesca Piazzolla (SL-20)
17:00-17:15 h	Volodymyr Kysil (SL-21)
17:15-17:30 h	Jurriën W. Collet (SL-22)

Thursday, August 30	
	Chair: Jörg Pietruszka
09:00-09:50 h	Dennis G. Hall, University of Alberta, Canada (PL-04)
09:50-10:20 h	Kirsten Zeitler, Universität Leipzig, Germany (IL-21)
10:20-10:35 h	Marvin Mantel (SL-23)
10:35-10:50 h	Nadine Zumbrägel (SL-24)
10:50-11:05 h	Chiara Lambruschini (SL-25)
11:05-11:35 h	Coffee break
	Chair: Luca Banfi
11:35-12:05 h	Rongrong Hu, Hongkong South China University of Technology, P. R. China (IL-22)
12:05-12:20 h	Asuncion Barbero (SL-26)
12:20-12:35 h	Natalia I. Guranova (SL-27)
12:35-12:50 h	Yi He (SL-28)
12:50-13:05 h	Anton V. Dolzhenko (SL-29)
13:00-14:00 h	Lunch break
15:30-18:30 h	Excursion
18:30-23:00 h	Boat trip and conference dinner

Friday, August 31	
	Chair: Ludger A. Wessjohann
09:00-09:50 h	Yanguang Wang, Zhejiang University, P. R. China (PL-05)
09:50-10:20 h	Michael A. R. Meier, KIT, Karlsruhe, Germany (IL-23)
10:20-10:35 h	Osama El-Sepelgy, RWTH-Aachen.de (SL-30)
10:35-10:50 h	Xiao-Feng Wu (SL-31)
10:50-11:20 h	Coffee break
	Chair: Thomas J. J. Müller
11:20-12:05 h	Lutz F. Tietze, Georg-August-Göttingen, Germany (PL-06)
12:05-12:30 h	Poster prizes, MCR 8, Closing remarks
12:30-13:30 h	Lunch break

General Information and Map

Location

The meeting will be held at lecture hall 3D in building 23.01 (see attached maps).

1. The registration and welcome reception will be right at the entrance to the building marked in the attached map.
2. To get to the lecture hall, exhibition and poster presentation, walk down the stairs directly opposite of the entrance and turn to the right. You will already see the conference location.

Welcome Reception

Beer and Prezels will be provided during the welcome reception.

Coffeebreak

Coffee, tea, mineral water and cockies will be provided during the coffee break.

Lunch

Lunch will be at the university dinning hall (Mensa). It is included in the conference fee. You will only have to show your MCR2018 batch and you can choose anything the university dinning hall has on offer. The university dining hall is 5 min by foot from the MCR2018 location (see attached maps).

A print out of the menu in english will be provided during the conference.

Poster Session

Beer and Prezels will be provided during the poster session.

Transportion

1. Public Transportation

   Public transportation to campus is rather convinient.

   a. You can either use tram 704, or subway U73 or U79 to Universität Ost/Botanischer Garten (University East/Botanical Garden). This is the terminal stop of these lines. Please note, that the subway lines run underground only in downtown Düsseldorf, on campus they are above.

b. Alternatively you can use the bus lines SB56, SB57, 731, 827, 835 and 836 to Universtität Mitte (University Center). This bus stop is located beside the only lake on campus.
c. To find the best connection to campus please use the following webpage: http://www.rheinbahn.com/Seiten/default.aspx. On the right side of the page you will find a form in order to find a connection. Please enter one of the stops on campus mentioned above and a stop close to your hotel (I am sorry, but in order to find the best connection you have to search twice).

2. By Car

   The address for the whole university is Universitätsstraße 1 in Düsseldorf. In case of problems with typing the umlaute (ä, ü, ß) please use either Universitatsstrasse 1 in Dusseldorf or Universtaetsstrasse 1 in Duesseldorf (replace the ä by either ae or a, the ü bei either ue or u and the ß by ss).

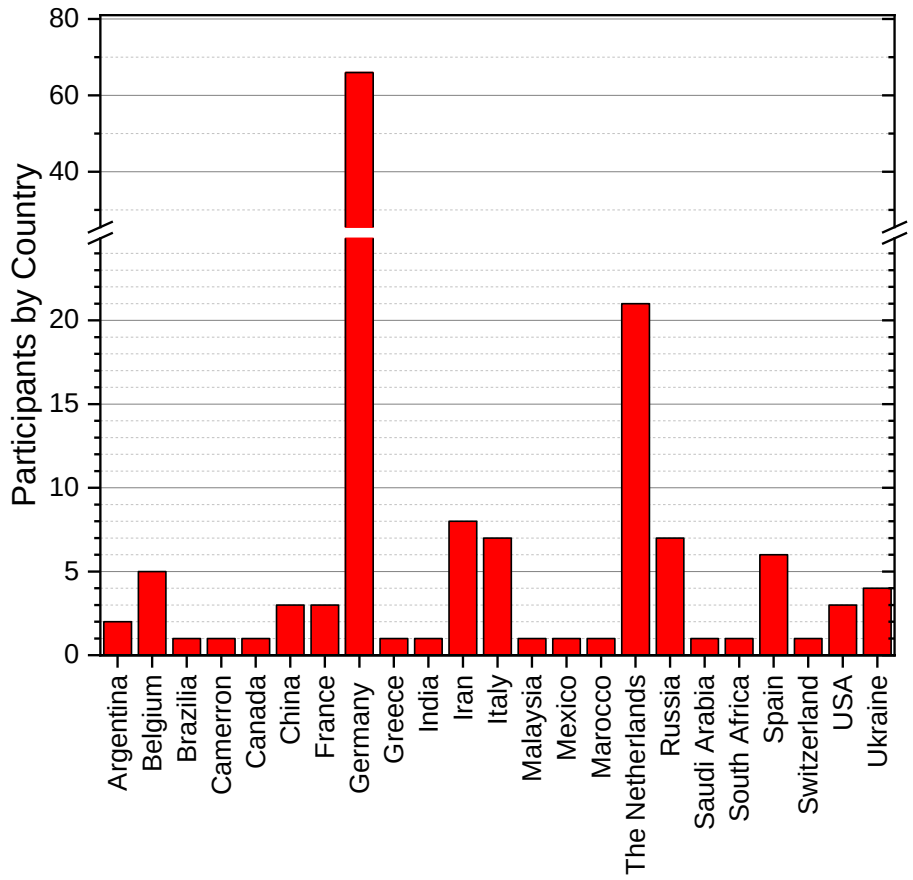
   On campus you have to look for parking P3 or P4. P3 is a normal parking lot, P4 is a garage. Both are free of charge and you should not have any problem to find a spot. The normal entrance to P4 is closed due to construction and you have to go through P3. You will find signs pointing the way.

Excursion and Conference Dinner

The excursion will be a sight-seeing tour through downtown Düsseldorf. We will arrange meeting points in the city. More details will be announced during the meeting.

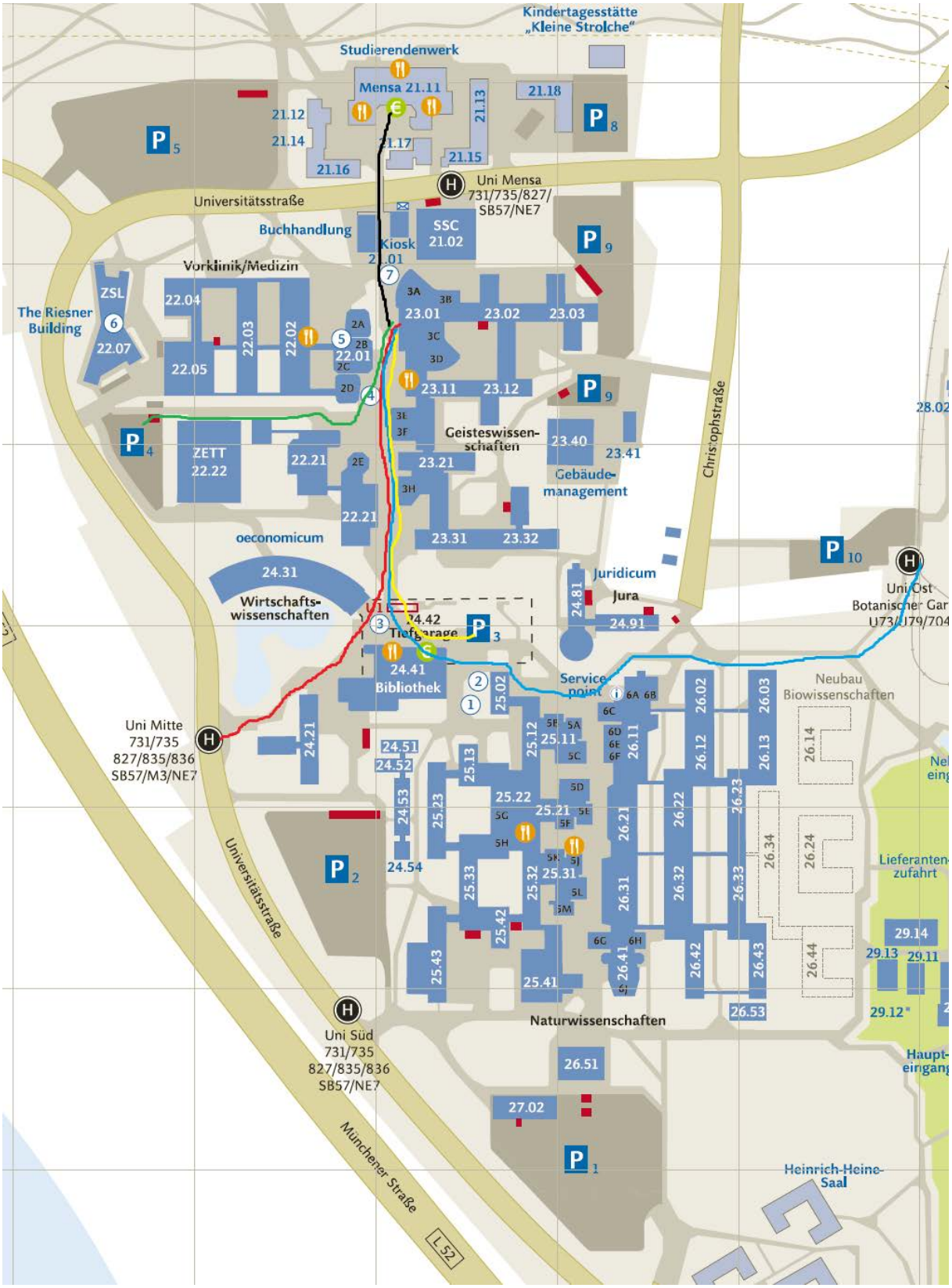
After the sight seeing tour is finished we will meet at a boat for a trip on the river Rhine. The meeting point is in down town Düsseldorf as well.

Participants by Country



Map (see next page)

- Path to bus stop Universität Mitte (university center) in red.
- Path to tram/subway terminal stop Universität Ost/Botanischer Garten (university east) in blue.
- Path to parking lot P3 in green.
- Path to parking garage P4 in yellow.
- Path to the Mensa (dinning hall) in black.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Heinrich-Heine-Saal

Plenary Lectures

The Development of Catalytic Aldehyde-Alkyne-Amine (A^3-Couplings) and Related Reactions in Water

Chao-Jun Li

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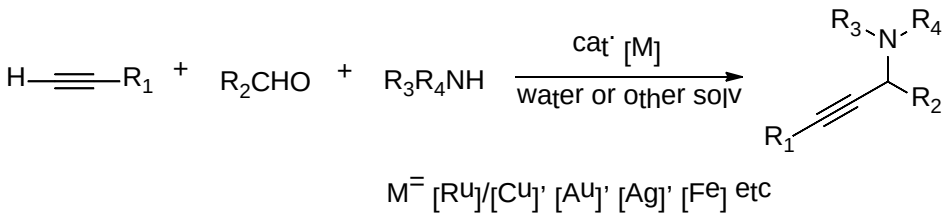
The reaction of metal acetylides with various electrophiles is a classic reaction in organic synthesis. Traditional methods of adding a nucleophilic alkyne involve the use of stoichiometric quantities of organo-magnesium or lithium reagents to generate highly nucleophilic and basic acetylide reagents via metallation of the acidic sp C-H bond of the alkyne. The reaction is generally carried out in an ether solvent, with limitations including the use of stoichiometric quantities of metal, sensitivity to air and water, and intolerance of various functional groups. To avoid such problems, we have been exploring various catalytic nucleophilic addition of alkynes in water. Among them is the multicomponent catalytic aldehyde-alkyne-amine catalyzed to generate propargyl amines. Many catalyztic systems such as [Ru]/[Cu], gold, silver, copper, iron and others were effective for such reactions. Carbohydrates can be used directly to generate the propagyl amine products. Multi A^3-reactions are also successful, which allows for the site-specific functionalization of amino acids and peptides under physiological conditions. Highly efficient asymmetric A^3-reactions involving both primary amines and secondary amines have also been succeeded. The reaction is also amenable for flow chemistry. This talk will highlight this development.



References:

1. Li, C. J., *Acc. Chem. Res.* **2010,** *43*, 581 - 590
2. Wei, C.; Li, Z.; Li, C.-J. *Synlett* **2004**, 1472-1483.
3. Yoo, W.-J.; Zhao, L.; Li, C.-J. *Aldrichimica Acta*, **2011**, *44*, 43-51.
4. Zani, L.; Bolm, C. *Chem. Commun.* **2006**, 4263.
5. Peshkov, V. A.; Pereshivko, O. P.; Van der Eycken, E. V. *Chem. Soc. Rev*. **2012**, *41*, 3702

MCRs and related one-pot processes using anhydrides: Discovery, Utility, Mechanism and Back Again

Jared T. Shaw

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Email: jtshaw@ucdavis.edu

A four-component reaction (4CR) discovered a decade ago will be described in terms of its synthetic utility, inspiration for new reactions, and detailed mechanistic analysis. This reaction exploits the dual reactivity of anhydrides as both electrophiles and nucleophiles. The original reaction spawned the development of several variants that have contributed to an understanding of the mechanism. Recently completed kinetic and theoretical studies have culminated in a detailed mechanistic picture that enables a fundamental revision of what was originally proposed. Recent efforts to use the complete mechanistic picture to design new MCRS will be discussed.

Multicomponent Reactions - Concepts and Applications

Magnus Rueping

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The development and application of sustainable multi-component reactions (MCRs) has become an increasingly important topic in chemistry, biotechnology and material sciences since MCRs allow the sustainable formation of products with high diversity and complexity in a combinatorial one-pot fashion. The challenges in designing and developing efficient MCRs for targeted synthesis are associated with the formation of by-products and, hence, the control of the individual bond forming events becomes a crucial factor. Thus, the successful development of MCRs will depend on the choice of reaction parameters and the catalysts employed.
In this presentation our introduction to MCRs will be shown and new and valuable transformations based on sustainable metal and organocatalysis will be highlighted. Additionally, efforts to delineate the general requirements for performing base metal and photoredox catalyzed MCRs and the applicability of these catalytic processes to the synthesis of bioactive products will be outlined.

Boron Based Multicomponent Reactions and Catalysts

Dennis G. Hall

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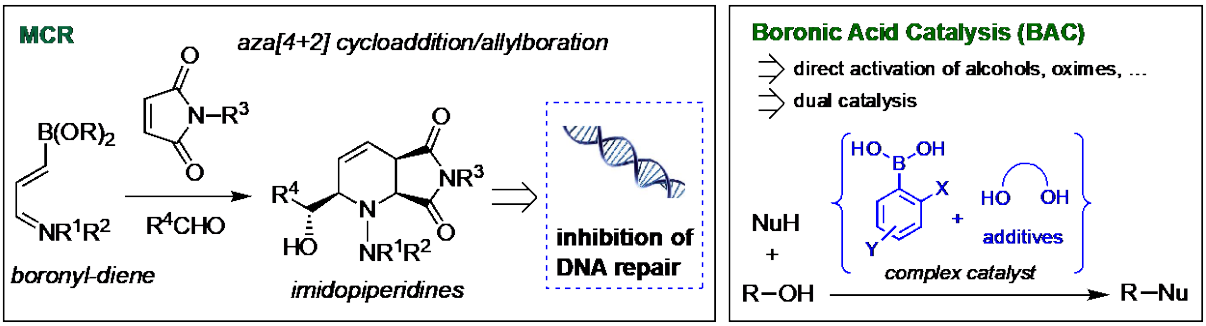
Advances in the preparation of organoboronic acid derivatives have greatly facilitated their use in the design of new multicomponent reactions (MCR) and catalysts, which in turn can enable new opportunities in applied fields, such as medicinal chemistry. The aza[4+2] cycloaddition/allylboration MCR was first optimized in our laboratory using 4-boronyl-hydrazonobutadienes, *N*-substituted imides, and aldehydes.[1] It was exploited in the preparation of combinatorial libraries of polysubstituted imidopiperidines that feature as many as four elements of chemical diversity. Biological screening of these drug-like imidopiperidine libraries unveiled the first reported inhibitors of the human DNA repair enzyme, polynucleotide kinase-phosphatase (hPNKP), thus opening a new strategy for cancer chemotherapy based on radiosensitization of malignant cells. From reaction design and development to preclinical evaluation and animal studies of a lead compound, this enterprise provides a strong demonstration of the value and importance of new MCRs.

The dynamic nature of boronic ester formation with polyols, along with the Lewis acid-base equilibrium involving ionic species, present further opportunities to develop complex multicomponent catalytic systems and dual-catalyzed reactions. Recently, organoboronic acids have also been employed as catalysts in the emerging field of "Boronic Acid Catalysis" (BAC).[2] By exploiting the reversibility of B–O bonds, BAC provides a unique strategy for the organocatalytic activation of hydroxyl functional groups. It features mild conditions, without the need for stoichiometric amounts of activating groups and reagents, leading to the direct transformation of alcohols and carboxylic acids into useful products with water as the sole by-product. In these systems, boronic acid, diol, and counter-anion all combine to afford more active catalysts. Tuning these parameters allows for the acceleration and expansion of the scope of important organic reactions such as direct Friedel-Crafts alkylations of alcohols, Beckmann rearrangement of oximes, and other processes involving hydroxyl-containing substrates.



References:
1 D. G. Hall, T. Rybak, T. Verdelet, *Acc. Chem. Res.* **2016**, *49*, 2489.
2 H. Zheng, D. G. Hall, *Aldrichimica Acta* **2014**, *47*, 41.

Reactions of Metal Carbenes Derived from 3-Diazoindolin-2-imines and 4-Diazoisochroman-3-imines

Yanpeng Xing, Guorong Sheng, Hualong Ding, Anni Ren, Bo Lang, Zhenmin Li, Kai Huang, Jin Qian, Fanghui Ma, Jie Qi, Ping Lu, Yanguang Wang

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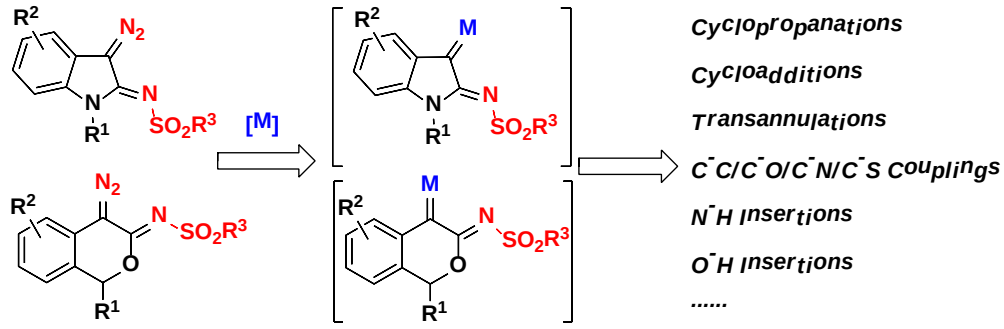
The quest for the discovery of new and powerful synthetic methods has been at the forefront of organic chemistry research for more than a century. These synthetic methods can connect readily accessible building blocks and become enabling technologies with broad impact beyond the field of organic chemistry. The metal-catalyzed decomposition of diazo compounds to generate transient metal carbenes has been exploited in a variety of useful synthetic transformations. The reactivity profile of metal carbenes is dependent on their structures. Generally, donor/acceptor-substituted carbenes are more chemoselective than carbenes that are substituted with only acceptor groups because the donor group (EDG) modulates the reactivity of the metal carbene. Consequently, a wide array of recent synthetic advances in this area has been achieved using donor/acceptor carbenes. Herein, we reported a novel class of donor/acceptor-substituted metal carbenes derived from cyclic dizao compounds. Thus, 3-diazoindolin-2-imines[1] and 4-diazoisochroman-3-imines[2] were conveniently prepared from readily available materials. These new class of diazo compounds were used as precursors of metal carbenes that underwent a variety of metal-catalyzed transformations, such as cyclopropanations, formal [3+2], [3+3] and [3+4] cycloadditions, transannulations, C-C/C-O/C-N/C-S couplings, and N-H/O-H insertions, affording a broad range of valuable indole and isochromene derivatives, respectively.[1,3]



References:

1 (a) Y. P. Xing, G. R. Sheng, J. Wang, P. Lu, Y.G. Wang, *Org. Lett*. **2014**, *16*, 1244. (b) G. R. Sheng, K. Huang, Z. H. Chi, H. L. Ding, Y. P. Xing, P. Lu, Y. G. Wang, *Org. Lett*. **2014**, *16*, 5096.

2 A. N. Ren, P. Lu, Y. G. Wang, *Chem. Commun.* **2017**, *53*, 3769.

3 (a) H. L. Ding, S. L. Bai, P. Lu, Y. G. Wang, *Org. Lett.* **2017**, *19*, 4604. (b) A. N. Ren, B. Lang, J. L. Lin, P. Lu, Y. G. Wang, *J. Org. Chem.* **2017**, *82*, 10953 (c) G. R. Sheng, K. Huang, S. C. Ma, J. Qian, P. Lu, Y. G. Wang, *Chem. Commun.* **2015**, *51*, 11056. (d) B. Lang, H. T. Z. Zhu, C. Wang, P. Lu, Y. G. Wang, *Org. Lett.* **2017**, *19*, 1630. (e) J. Qian, G. R. Sheng, K. Huang, S. J. Liu, P. Lu, Y. G. Wang, *Org. Lett.* **2016**, *18*, 3682. (f) Z. M. Li, X. R. Zhou, P. Lu, Y. G. Wang, *J. Org. Chem.* **2016**, *81*, 9433.

Multicomponent Domino Reactions in the Green Synthesis of Natural Products and Materials

Lutz F. Tietze

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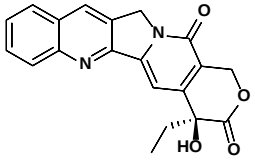
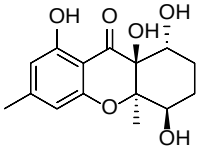
The efficient synthesis of natural products, drugs, agrochemicals and materials is a very important aspect in academia and industry. To allow an ecologically and economically favourable approach in a green fashion the former stepwise procedures must be replaced by domino reactions which allow the preparation of complex molecules starting from simple substrates in a straight forward way. Domino reactions[1] allow the reduction of the amount of waste being formed and the preservation of our resources. Moreover, they are also favourable in an economical way since they consume less time.



Camptothecin



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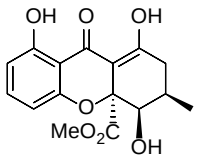
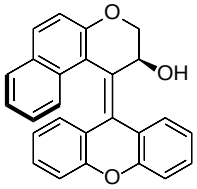


(-)-Blenolid A



Molecular Switches

The usefulness of the domino multicomponent concept is demonstrated with the synthesis of alkaloids using a domino-Knoevenagel/hetero-Diels-Alder reaction[2] and fungal metabolites[3,4] using an enantioselective domino-Wacker/carbonylation/methoxylation reaction. The approach has also been applied for the synthesis of novel materials such as molecular switches[5] and fluorescence dyes[6] using a domino-Sonogashira/carbopalladation/CH-activation reaction.

References:

(1) a) Domino Reactions: Concepts for Efficient Organic Synthesis, Ed.: L. F. Tietze, Wiley-VCH, Weinheim, **2014**; b) L.F. Tietze, G. Brasche, K. Gericke: Domino Reactions in Organic Synthesis, Wiley-VCH, Weinheim **2006**; b) L.F. Tietze, *Chem Rev*. **1996**, *96*, 115-136.

(2) L.F.Tietze, M. Bischoff, T.A. Khan, D. Liu *Chem. Heterocycl. Comp.* **2017**, *53*, 434-445.

(3) a) L. F. Tietze, D. A. Spiegl, F. Stecker, J. Major, C. Raith, C. Grosse, *Chem. Eur. J.* **2008**, *14*, 8956-8963; b) L. F. Tietze, S. Jackenkroll, C. Raith, D. A. Spiegl, J. R. Reiner, M. C. Ochoa Campos, *Chem. Eur. J.* **2013**, *19*, 4876-4882 c) L. F. Tietze, L. Ma, J.R. Reiner, S. Jackenkroll, S. Heidemann, *Chem. Eur. J.* **2013**, *19*, 8610-8614; d) L. F. Tietze, S. Jackenkroll, J. Hierold, L. Ma, B. Waldecker, *Chem. Eur. J.* **2014**, *20*, 8628-8635.

(4) a) D. Ganapathy, J.R. Reiner, L.E. Löffler, L. Ma, B. Gnanaprakasam, B. Niepötter, I. Koehne, L.F. Tietze *Chem. Eur. J.* **2015**, *21*, 16807-16810; b) D. Ganapathy, J.R. Reiner, G. Valdomir,S. Senthilkumar, L.F. Tietze *Chem. Eur. J.* **2017**, *23,* 2299-2302.

(5) a) L. F. Tietze, M. A. Düfert, F. Lotz, L. Sölter, K. Oum, T. Lenzer, T. Beck, R. Herbst-Irmer, *J. Am. Chem. Soc.* **2009**, *131*, 17879-17884; b) L. F. Tietze, M. A. Düfert, T. Hungerland, K. Oum, T. Lenzer, *Chem. Eur. J.* **2011**, *17*, 8452-8461; c) L. F. Tietze, T. Hungerland, M. A. Düfert, I. Objartel, D. Stalke. *Chem. Eur. J.* **2012**, *18*, 3286-3291; d) L. F. Tietze, T. Hungerland, C. Eichhorst, A. Düfert, C. Maaß, D. Stalke, *Angew. Chem., Int. Ed.* **2013**, *52*, 3668-3671; e) T. A. Khan, T. Fornefeld, D.Hübner, P. Vana, L. F. Tietze, *OrgLett,* **2018**.

(6) a) L. F. Tietze, C. Eichhorst, T. Hungerland, M. Steinert, *Chem. Eur. J.* **2014**, *20*, 12553-12448; b) L. F. Tietze, C. Eichhorst, *Heterocycles* **2015**, *90*, 919-27.

Invited Lectures

20 Years of MCR Chemistry in the Dömling Laboratory

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I was very privileged to have performed my PhD under the late Ivar Ugi (1935-2005). He is my role model of an outstanding teacher and scientist. Ivar Ugi was a visionary scientist who created and influenced trends in science and foresaw their applications in industry and their usefulness for society, many years before anyone else. For example, through the introduction of the four component reactions and their early applications (e.g. lidocaine synthesis) he paved the way for an important area of chemistry: combinatorial chemistry. Indispensable for the creation of bioactive compounds and recently having a renaissance in DNA-encoded library generation (DEL). Another field Ivar Ugi was pioneering is computational reaction design, see for example a recent work published in NATURE: Planning chemical syntheses with deep neural networks and symbolic AI. Now one of the hottest areas in synthetic chemistry and called artificial intelligence directed synthesis. Like no other scientist he influenced my academic and industrial career and the topics and areas I was working on since performing my PhD.[1]
In my talk I will give an overview of my laboratories work in US and Europe in MCR chemistry[2] and highlight applications on reaction and scaffold design,[3] PNA and sequence defined polymer synthesis,[4] imaging agents,[5] pharmacophore and MCR-based computational platform ANCHOR-QUERY,[6] structure-based drug design,[7] antibody drug conjugate,[8] artificial macrocycles[9] and drug discovery at the speed of sound.[10]

References:

1 A. Dömling, I. Ugi, *Angew. Chem. Int. Ed.* **2000**, *39*, 3168.
2 A. Chandgude, T. Tzitzikas, A. Dömling *Chem. Rec.* **2015**, *15*, 981.
3 P. Patil et al. *Org. Lett.* **2017**, *19*, 642.
4 K.Z. Chi, A. Dömling, M. Barrère, *Bioorg. Med. Chem. Lett.* **1999**, *9,* 2871.
5 A. Boltjes et al. *Chem. Eur. J.* **2016**, *22*, 7352.
6 D.R. Koes, A. Dömling, C.J. Camacho, *Protein Sci.* **2017**, *27*, 229.
7 K Guzik et al. *J. Med. Chem.* **2017**, *60*, 5857.
8 T M Vishwanath et al. Poster MCR-2018.
9 R. Madhavachary, E.M.M. Abdelraheem et al. *Angew. Chem. Int. Ed. Engl.* **2017**, *56*, 10725.
10 S. Shabaani et al. Poster MCR-2018.

Multicomponent Reactions Applied to Renewable Starting Materials

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An important contribution to the reduction of world's dependence on fossil carbon sources is the successful transformation of biomass into bio-based chemicals.[1] A whole new chemistry has to be developed, alternative to the classic organic synthesis, which starts mainly from mineral oil.[2] This chemistry will lead to new bio-based chemicals, not necessarily identical to those produced starting from oil. They could be in principle even superior, for example from the point of view of biodegradability. While up to now most efforts have been devoted to the preparation of high volume - low cost commodities, the synthesis of high added value bio-based compounds, such as chemical specialties, Active Pharmaceutical Ingredients (APIs), drug candidates, organocatalysts, functional materials and so on, has been less explored. In this lecture, the recent efforts of my group[3] for developing new efficient and diversity-oriented routes from typical renewable building blocks to more complex, nitrogen containing, heterocycles, will be described. Multicomponent reactions (especially those based on isocyanides) have been the main methodological tool towards this goal, thanks to their clear advantages from the green chemistry point of view.[4] Apart from MCRs, we have made extensive use of biocatalysis for the obtainment of chiral enantiopure intermediates, and of electrophilic catalysis by a sustainable (low cost, low toxicity) metal ion like zinc for improving the stereoselectivity in some Passerini reactions performed on aldehydes derived from renewable building blocks.

References:

1 A. Corma, S. Iborra, A. Velty, *Chem. Rev.* **2007,** *107*, 2411.
2 N.D. Fitzgerald, *Nature Reviews Chemistry* **2017,** *1*.
3 V. Cerulli, L. Banfi, A. Basso, V. Rocca, R. Riva, *Organic and Biomolecular Chemistry*, **2012**, *10*, 1255. E. Tassano, A. Alama, A. Basso, G. Dondo, A. Galatini, R. Riva, L. Banfi, *Eur J. Org. Chem.*, **2015**, 6710. L. Moni, L. Banfi, A. Basso, E. Martino, R. Riva, *Org. Lett.*, **2016**, *18*, 1638. *Errata corrige:* 3306. L. Moni, L. Banfi, A. Basso, A. Bozzano, M. Spallarossa, L. Wessjohann, R. Riva, *Molecules*, **2016**, *21*, 1153. C. Lambruschini, D. Galante, L. Moni, F. Ferraro, G. Gancia, R. Riva, A. Traverso, L. Banfi, C. D'Arrigo, *Org. Biomol. Chem.*, **2017**, *15*, 9331.
4 R.C. Cioc, E. Ruijter, R.V.A. Orru, *Green Chem.* **2014**, *16*, 2958.

Towards Selective Multiple Multicomponent Reactions

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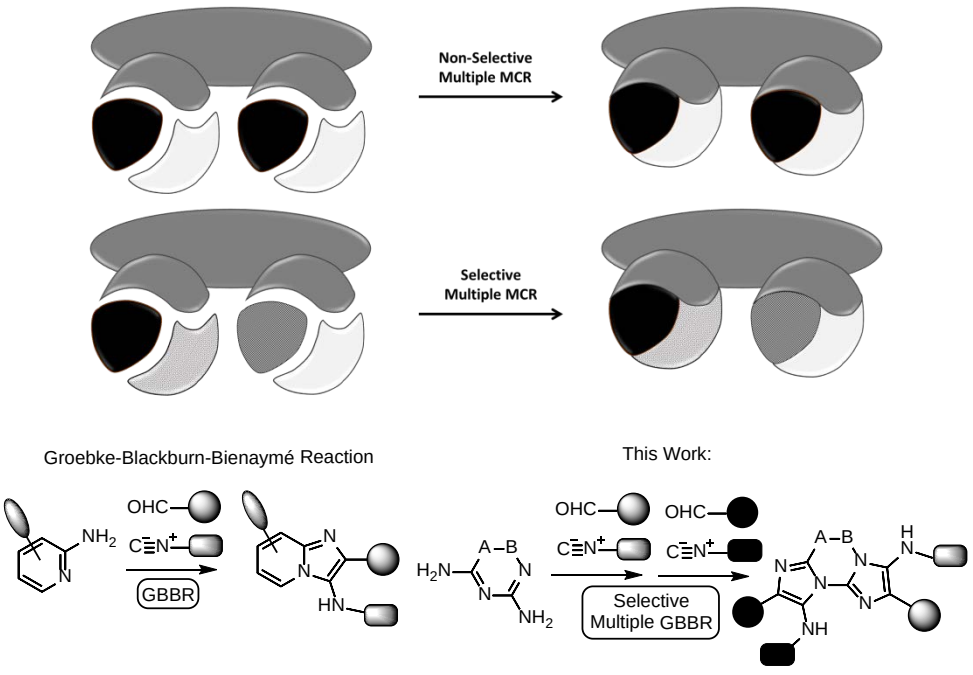
Multiple Multicomponent Reactions rapidly build large and complex structures.[1] However, their lack of selectivity, together with the reduced number of viable transformations restrict their application in organic synthesis.[2] We describe a rationale for selective Multiple Multicomponent Reactions, reaching connectivity patterns with unparalleled complexity in a fast manner. Our approach also expands the current options for these processes, mainly limited to Ugi and Passerini processes. Thus, a novel isocyanide-multiple MCR based in the Groebke-Blackburn-Bienaymé reaction was developed. Furthermore, the application of our reaction to biologically relevant cores (diaminopyrimidine, diaminopyridazine, melamine) leads in a direct and programmed way to a variety of complex adducts which display impressive performance as fluorophores, antiviral agents, and selective DNA quadruplex-binders. Notably, our protocol also constitutes a powerful synthetic entry for nanometric-sized compounds, potentially useful in a bottom-up approach for materials science. Finally, a computational study unravels the reasons for the selectivity in these systems and allows a generalization for the extension of this methodology.



References:

1 L. A. Wessjohann, R. A. Neves Filho, D. G. Rivera, in *Isocyanide Chemistry: Applications in Synthesis and Materials Science* (Ed. V. Nenajdenko), pp 233-262. Wiley-VCH, Weinheim, 2012.

2 S. Brauch, S. S. Van Berkel, B. Westermann, *Chem. Soc. Rev*. **2013**, *42*, 4948-4962

"Organocatalytic Enantioselective MCR from 1,3-Dicarbonyls: when b-Ketoamides surpass b-Ketoesters"

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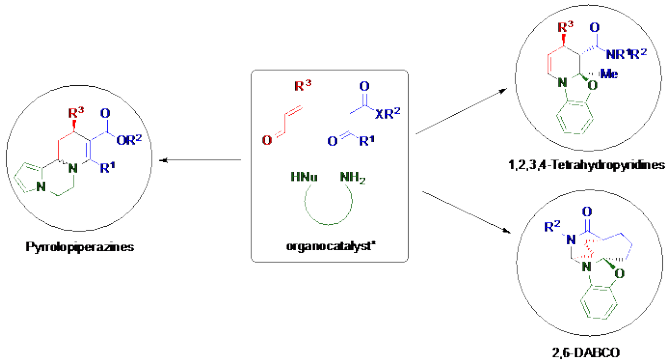
Our group is interested for several years in the synthesis of (poly)heterocyclic molecules *via* new selective Michael addition-initiated domino and multicomponent reactions involving a 1,2- or a 1,3-dicarbonyl compound,[1] a Michael acceptor and various amines. More recently, we focused our attention on the stereoselective outcome of these domino and multicomponent reactions, especially those involving ketoamides as substrates. In this context, we developed the first organocatalytic enantioselective conjugate addition of 1,2-[2] and 1,3-ketoamides[3] to unsaturated carbonyls or nitroolefins, using amino-thiourea bifunctional catalysts. An unprecedented cooperative effect of the amide function in the activation of these pronucleophiles has been evidenced.[4]

Within this oral presentation, a general perspective of the research program aimed towards the preparation of polycyclic heterocycles by the means of enantioselective organocatalytic MCR will be presented,[5] with a focus on the synthesis of pyrrolopiperazines,[6] 1,2,3,4-tetrahydropyridines[7] and polyfunctionalized molecules containing a 2,6-DABCO core.[8] Guidelines for reaction design, including the selection of substrates and organocatalysts will be discussed,[9] along with post-functionalizations to afford diversified heterocyclic scaffolds.



[1] a) D. Bonne *et al.*, *Chem. Eur. J.*, **2013**, *19*, 2218. b) X. Bugaut *et al.*, in *Multicomponent reactions in organic synthesis*, Eds: J. Zhu, Q. Wang, M.-X. Wang, Wiley-VCH, **2014**, Chap. 5, p. 109. c) C. Allais *et al.*, *Chem. Rev.*, **2014**, *114*, 10829, d) *Stereoselec-tive multiple bond-forming transformations in organic synthesis.* D. Bonne, J. Rodriguez Eds, Wiley-VCH, **2015**.
[2] O. Baslé *et al.*, *Org. Lett.,* **2010**, 12, 5246.
[3] M. M. Sanchez Duque *et al.*, *Org. Lett.,* **2011**, 13, 3296.
[4] A. Quintard *et al.*, *Chem. Eur. J.,* **2015**, 21, 778
[5] H. Du *et al.*, *Synthesis,* **2016**, 48, 3479.
[6] H. Du *et al.*, *Adv. Synth. Catal.,* **2014**, 356, 851.
[7] a) Y. Dudognon *et al.*, *Chem. Commun.,* **2015**, 51,1980 ; b) Y. Dudognon *et al.*, *Eur. J. Org. Chem.,* **2018**, just accepted.
[8] M. M. Sanchez Duque *et al.*, *Angew. Chem. Int. Ed.,* **2013**, 52, 14143.
[9] H. Du *et al.*, *Synlett,* **2018**, just accepted.

Peptide/Protein Labeling, Conjugation and Stapling by Multicomponent Reactions

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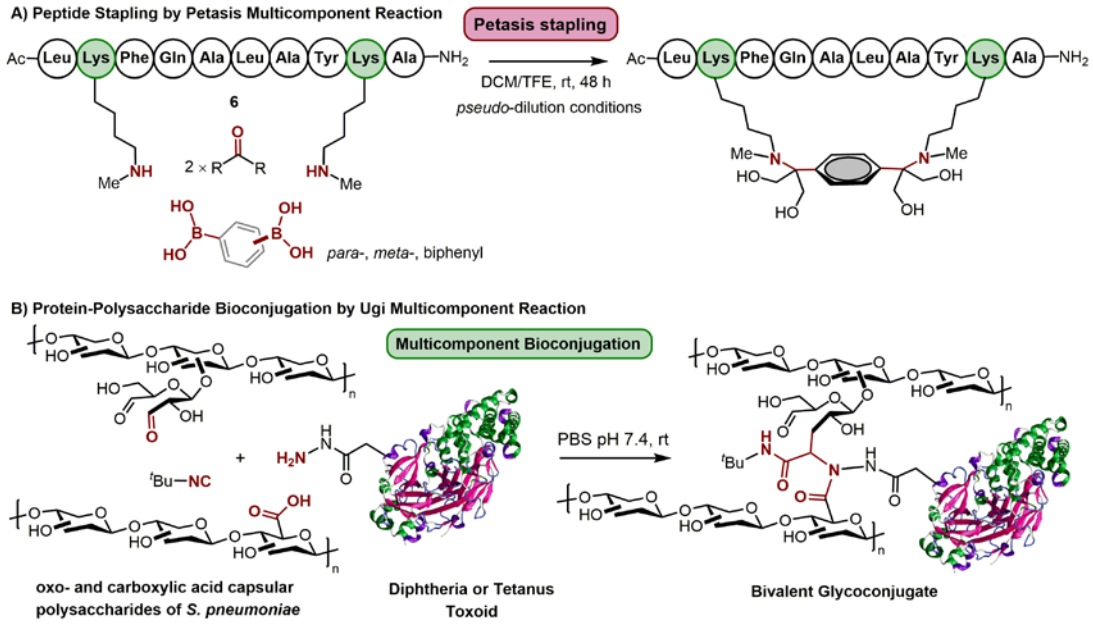
Multicomponent reactions have lately evolved from versatile methods for the synthesis of small molecules to powerful tools for the post-synthetic derivatization of peptides[1] and proteins.[2] This lecture highlights the most recent multicomponent transformations conducted at UH and IPB to covalently modify peptides and proteins. These transformations include the multicomponent labeling and stapling of peptides by means of the Petasis reaction as well as the utilization of the Ugi and Ugi-Smiles multicomponent reactions for the simultaneous lipidation/PEGylation and cyclization of peptides.[3] Finally, our recent endeavor on the development of antibacterial glycoconjugate vaccine candidates by means of a multicomponent polysaccharide-protein conjugation is described.[2]



References:

1 (a) C. J. White, A. K. Yudin, *Nature Chem.* **2011**, *3*, 509. (b) A. V. Vasco, C. S. Pérez, F. E. Morales, H. E. Garay, D. Vasilev, J. A. Gavín, L. A. Wessjohann, D. G. Rivera, *J. Org. Chem.* **2015**, *80*, 6697.

2 Y. Méndez, J. Chang, A. R. Humpierre, A. Zanuy, R. Garrido, A. V. Vasco, J. Pedroso, D. Santana, L. M. Rodríguez, D. García-Rivera, Y. Valdés, V. Vérez-Bencomo, D. G. Rivera, *Chem. Sci.* **2018**, *9*, 2581.

3 (a) M. C. Morejón, A. Laub, G. N. Kaluđerović, A. R. Puentes, A. N. Hmedat, A. J.; Otero-González, D. G. Rivera, L. A. Wessjohann, *Org. Biomol. Chem.* **2017**, *15*, 3628. (b) M. C. Morejón, A. Laub, B. Westermann, D. G. Rivera, L. A. Wessjohann, *Org. Lett.* **2016**, *18*, 4096.

Multicomponent Heterocyclizations Involving Aminoazoles and Salicylaldehydes with Controlled Chemoselectivity

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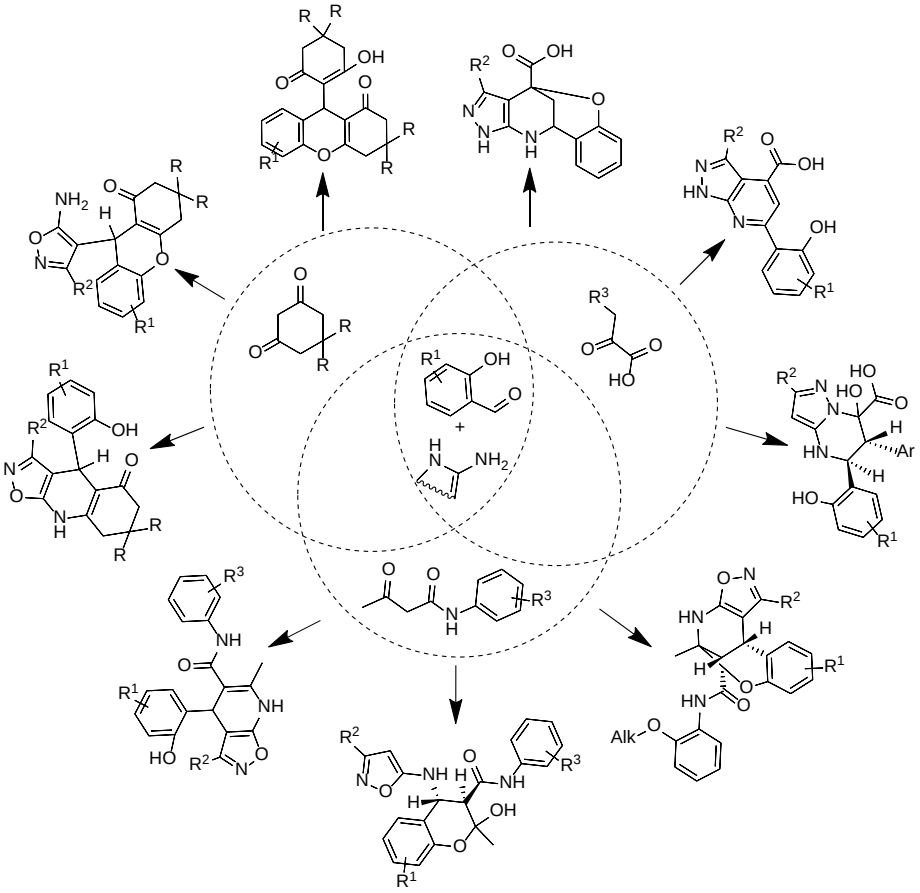
To control selectivity of multicomponent reaction the Condition-Based Divergent Strategy had been developed and applied for wide range of heterocyclizations, for instance, to switch directions of the treatments between carbonyl-containing CH-acids, aromatic aldehydes and aminoazoles.[1-3] An introduction of additional reactive functional groups into the starting reagents allows to increase diversity of final structures, therefore, we applied the Strategy to tune selectivity of the MCRs involving aminoazoles and salicylaldehydes (see Scheme) using conventional and non-classical methods of activation (microwave irradiation and ultrasonication) as well as different catalytic systems.



References:

1 V.A. Chebanov, S.M. Desenko, *Chem. Heterocycl. Comp.*, **2012**, *48*, 566-583.
2 V.A. Chebanov, S.M. Desenko, *Diversity Oriented Synthesis*, **2014**, *1*, 43-63.
3 E. Ruijter, R. Scheffelaar, R.V.A. Orru, *Angew. Chem. Int. Ed. Engl.*, **2011**, *50*, 6234-6246.

Discovery of the Clinical Candidate Ribuvaptan, a Dual Acting Vasopressin V1a/V2 Receptor Antagonist for the Treatment of Heart Failure

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[1]Medicinal Chemistry, [2]Research Pharmacokinetics, [3]Cardiovascular Research, [4]Lead Discovery, [5]Biomarker Research, [6]Experimental Medicine CV

Congestive heart failure (CHF) is a severe chronic disease which usually progresses steadily towards death, despite recent therapeutic advances. In CHF, the peptide hormone vasopressin is increased in plasma and the associated fluid retention has been shown to be a prognostic factor in this patient population [1,2,3]. Elevated vasopressin levels mediate deleterious effects via two different GPCRs: vascular V1a and renal V2 receptors. Selective V2 receptor antagonism has proven short-term beneficial effects (i.e. body weight loss due to aquaresis), but leads to compensatory increased vasopressin levels which might activate unprotected V1a receptors.

In our hypothesis, a dual acting V1a/V2 antagonist should blunt V1a-mediated effects expected with chronically elevated vasopressin levels (i.e. peripheral vasoconstriction and reduced cardiac output) while maintaining the favorable decongestive effects of V2 antagonism [4, 5].

A recombinant cell line expressing the human V1a receptor was used for high throughput screening delivering triazolones as a novel structural motif for vasopressin receptor blockers with IC_{50}s both on the V1a and the V2 receptor in a range of 100 - 300 nM. Initial optimization efforts were focused on increasing potency on both the V1a and the V2 receptor and on enhancing metabolic stability. Despite the potent inhibition of the V2 receptor and increased metabolic stability, only moderate activity was seen in vivo in the rat diuresis model after oral administration most likely due to limited absorption of the compounds. In addition, many compounds exhibited a strong drug-drug interaction potential. Significant improvements in potency on both receptors and oral absorption could be achieved by replacing a cyclopropyl substituent by a trifluoromethylhydroxyl substituent. The overall increase in polarity in the course of the following optimization rounds further improved metabolic stability. Finally, Ribuvaptan was identified as a novel potent, dual acting V1a/V2 receptor antagonist with excellent pharmacokinetic properties. Its characterization includes various in vivo diuresis models in rats as well as a heart failure model in paced dogs.

The prediction of human PK parameters based on an allometric scaling approach as well as the predicted minimal effective dose in humans based on rat diuresis data translate reasonably well to observed PK/PD data from single and multiple dose studies in healthy volunteers.

[1]: Goldsmith, S.R et al. J. Am. Coll. Cardiol. 1986; 8: 779-783
[2]: Francis, G.S. et al. Circulation 1990; 82: 1724-1729
[3]: Roleau, J.L. et al. *J. Am. Coll. Cardiol.* 1994; 24: 583-591
[4]: Udelson, J.E. et al. *Circulation* 2001; 104 : 2417-2423
[5]: Mondritzki T et al. *Am J Ther.* 2011 ; 18(1):31-37

Development of bioactive molecules using the tools of chemical synthesis

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Production of molecules with desired functional attributes is the enduring objective of chemical synthesis. As structural complexity of therapeutic agents increases, so is the number of interrelated parameters that need to be controlled. Bioactive macrocycles offer a good example underscoring this notion. Their relatively large polar surface area increases the chance to interrogate extended protein binding sites, but also creates an impediment to achieving favorable drug properties. Synthetic tools that allow one not only to cyclize linear precursors but also to exercise control over conformation-driven cellular permeability are in high demand. This part of the lecture will summarize our ongoing efforts in this area and will highlight key experimental findings obtained in the past few months.

Another active area of our research targets biologically active boron-containing molecules. Boron is an abundant element on earth yet, despite its availability, C-B bonds are not present in the structures of natural products. This, however, does not mean that boron has no utility in chemical biology and drug discovery. On the contrary, there are numerous examples of bioactive molecules that bear C-B bonds. Similar to the synthetic utility of organoboron compounds, the biological activity of boron-containing molecules is based on reversible covalent interactions with nucleophiles. I will present the foundational principles of *Boroscan* – an enabling technology to construct boron-containing bioactive molecules using amphoteric molecules.

References:

1 Frost, J.; Scully, C. C. G.; Yudin, A. K. “Oxadiazole Grafts in Peptide Macrocycles,” *Nat. Chem.* **2016**, *8*, 1105-1111.
2 Diaz, D. B.; Yudin, A. K. “The versatility of boron in biological target engagement,” *Nat. Chem.* **2017**, 9, 731-742.
3 Tan, J.; Cognetta, A. B. III; Diaz, D. B.; Lum, K. M.; Adachi, S.; Kundu, S.; Cravatt, B. F.; Yudin, A. K. *Nat. Commun.* **2017**, DOI: 10.1038/s41467-017-01319-4.

Multicomponent perfluoroalkylation Reactions by Visible-Light Photoredox Catalysis

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Organofluorine compounds play a major role in the fields of life sciences, agrochemicals and materials.[1] Due to the unique properties of CnF_m-containing compounds, it is highly significant to develop direct and efficient methods to incorporate the perfluoralkyl group into organic skeletons.[1] However, the synthesis of a fluorinated molecule is still far from obvious. This is especially true if the incorporation of the perfluorinated moiety occurs at a late stage of the synthesis of a highly functionalized compound. While substantial progress has been made in this regard during the ten last years, the development of efficient perfluoroalkylation methods remains an attractive goal.

In this symposium, we will present our recent contributions in the development of visible-light photocatalytic multicomponent methods for the introduction of a variety of fluoroalkyl groups to olefins.[3] In addition, our recent efforts in the synthesis of new electrophilic perfluoroalkylating reagents in photoredox catalysis will be detailed.[4]

References:

1 (a) P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, Wiley-VCH: Weinheim, 2004. (b) K. Müller, C. Faeh, F. Diederich, Science **2007**, *317*, 1881. (c) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320.

2 (a) T. Koike, M. Akita, *Top. Catal*. **2014**, *57*, 967. (b) H. Egami, M. Sodeoka, *Angew. Chem., Int. Ed.* **2014**, *53*, 8294. (c) C. Alonso, E. Martínez de Marigorta, G. Rubiales, F. Palacios, *Chem. Rev.* **2015**, *115*, 1847.

3 (a) A. Carboni, G. Dagousset, E. Magnier, G. Masson, *Org. Lett.* **2014**, *16*, 1240. (b) G. Dagousset, A. Carboni, E. Magnier, G. Masson,. *Org. Lett.* **2014**, *16*, 4340. (c) A. Carboni, G. Dagousset, E. Magnier, G. Masson, *Chem. Comm.* **2014**, *50*, 14197. (d) A. Carboni, G. Dagousset, E. Magnier, G. Masson, *Synthesis* **2015**, *47*, 2439. (e) L. Jarrige, A. Carboni, G. Levitre, G. Dagousset, E. Magnier, G. Masson, *Org. Lett.* **2016**, *18*, 2906.

4 M. Daniel, G. Dagousset, P. Diter, P.-A. Klein, B. Tuccio, A.-M. Goncalves, G. Masson, E. Magnier, *Angew. Chem. Int. Ed.* **2017**, *56*, 3997.

Discovery of Finerenone - A Nonsteroidal Antagonist of the Mineralocorticoid Receptor for the Treatment of Cardiorenal Diseases

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Aldosterone is a hormone that exerts manifold deleterious effects on the kidneys, blood vessels, and heart which can lead to pathophysiological consequences. Inhibition of the mineralocorticoid receptor (MR) is a proven therapeutic concept for the management of associated diseases. Use of the currently marketed MR antagonists spironolactone and eplerenone is restricted, however, due to a lack of selectivity in spironolactone and the lower potency and efficacy of eplerenone. Several pharmaceutical companies have implemented programs to identify drugs that overcome the known liabilities of steroidal MR antagonists. Herein a SAR exploration starting from cyano-1,4-dihydropyridines that were identified by high-throughput screening is disclosed. The efforts led to the identification of the dihydronaphthyridine, Finerenone, which is a potent, selective, and orally available nonsteroidal MR antagonist currently under investigation in a clinical phase III trial. Selected preclinical and clinical data will be shown.

New Facets and Applications of the Formal [2+4] Cycloaddition of Imines and Dicarboxylic Acid Anhydrides (the Castagnoli-Cushman Reaction)

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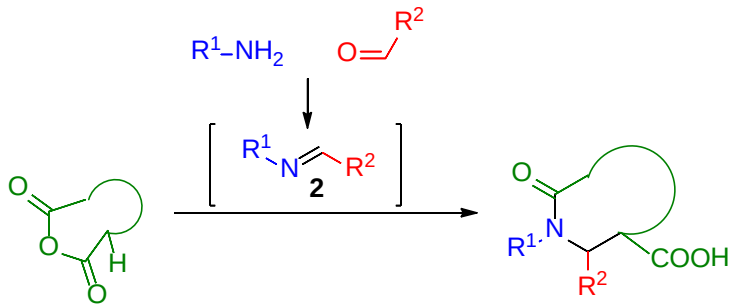
The formal [2+4] cycloaddition of imines and α-C-H dicarboxylic acid anhydrides (cyclic anhydrides) has proven itself as a remarkably efficient method of accessing polysubstituted δ- and γ-lactams. Despite the fact that the reaction has been known for over 45 years now,[1-2] certain aspects of its scope and practical format remained underdeveloped. In particular, the diversity of cyclic anhydrides[3] clearly could receive some attention in terms of expansion. Likewise, despite being a multicomponent reaction by spirit, the Castagnoli-Cushman reaction was seldom conducted by mixing all three reagents together, imine is typically pre-formed prior to addition of the cyclic anhydride component. Cyclic anhydrides themselves represent a liability due to labile hydrolytic character. Yet, approaches based *on situ* dehydration of a dicarboxylic acid were not explored for long time.[4]
The Castagnoli-Cushman chemistry delivers excellent, high-sp^3, stereodefined compounds that appear to be highly suitable for drug design applications. In this talk, we will present recent biomedical applications of this chemistry validated in our laboratories.



References:

1 N. Castagnoli, *J. Org. Chem.* **1969**, *34*, 3187−3189.
2 M. Cushman, N. Castagnoli, *J. Org. Chem.* **1973**, *38*, 440−448.
3 M. Krasavin, D. Dar'in, *Tetrahedron Lett.* **2016**, *57*, 1635-1640.
4 A. Lepikhina, D. Dar'in, O. Bakulina, E. Chupakhin, M. Krasavin, *ACS Comb. Sci.* **2017**, *19*, 702-707.

Post-condensations of Ugi and Passerini adducts; a step towards higher diversity

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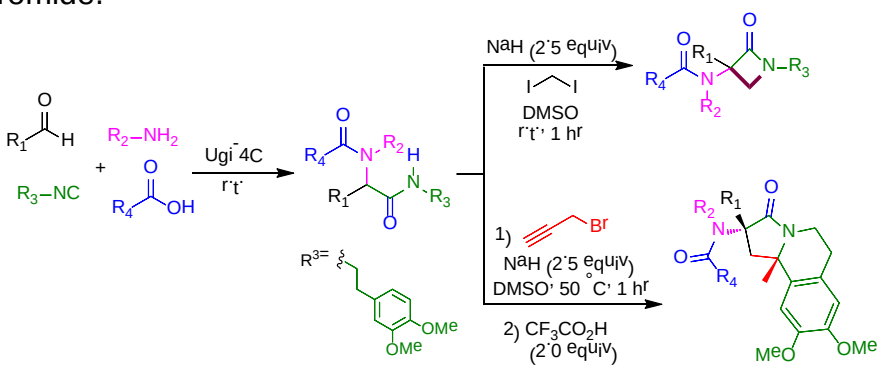
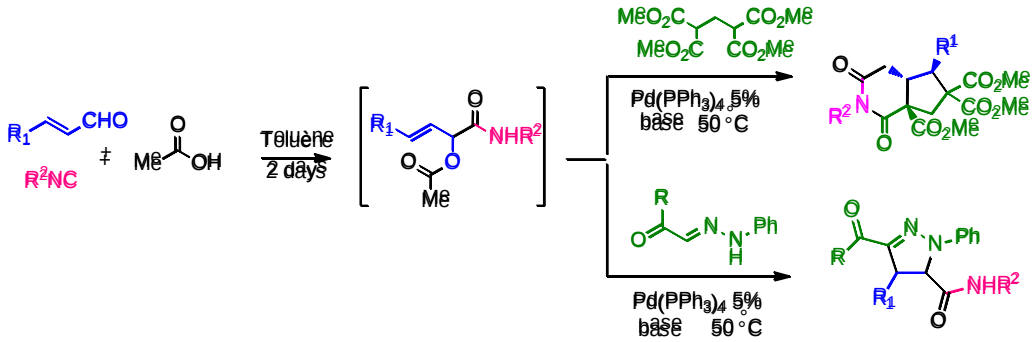
Ugi and Passerini Post-condensations are modifications of Ugi and PAsserini adducts that traditionally involve intramolecular reactions leading to more or less complex heterocyclic scaffolds. We have been interested in the last few years by performing intermolecular reactions playing both on the peptidyl positions of Ugi adducts and on Palladium based transformations of cinnamaldehyde Passerini adducts. In the case of Ugi adducts, the formation of amide dianions has allowed us to achieve easy room temperature alkylations which have been extended to the disclosure of cascades using bielectrophilic derivatives such as diiodomethane or propargyl bromide.[1]



The use of cinnamaldehyde in Passerini reaction represents an interesting opportunity to disclose various Tsuji-Trost based cascade taking advantage of the intermediate formation of α,β-unsaturated amides which may be involved in further Michael type additions.[2]



References:

1 (a) A. Zidan, J. Garrec, M. Cordier, A. M. El Naggar, N. E. A. El-Sattar, A. K. Ali, M. A. Hassan, L. El Kaïm, *Angew. Chem Int. Ed,* **2017,** 56, 12179. (b) A. Zidan, M. Cordier, A. M. El-Naggar, N. E. A. Abd El-Sattar, M. Ali Hassan, A. Khalil Ali, L. El Kaïm, *Org. Lett.*, **2018**, accepted, 10.1021/acs.orglett.8b00687

2 M. Cordier, A. Dos Santos, L. El Kaïm, N. Narboni, *Chem. Commun.*, **2015**, 51, 6411. E. H. El Mamouni, M. Cattoen, M. Cordier, J. Cossy, S. Arseniyadis, H. Ilitki, L. El Kaïm, *Chemical Communications*, **2016**, *52*, 14490. N. Narboni, L. El Kaim**,** *Eur. J. Org. Chem*. **2017**, 4242.

Synthesis of (macro)heterocycles by consecutive isocyanide-based multicomponent reactions

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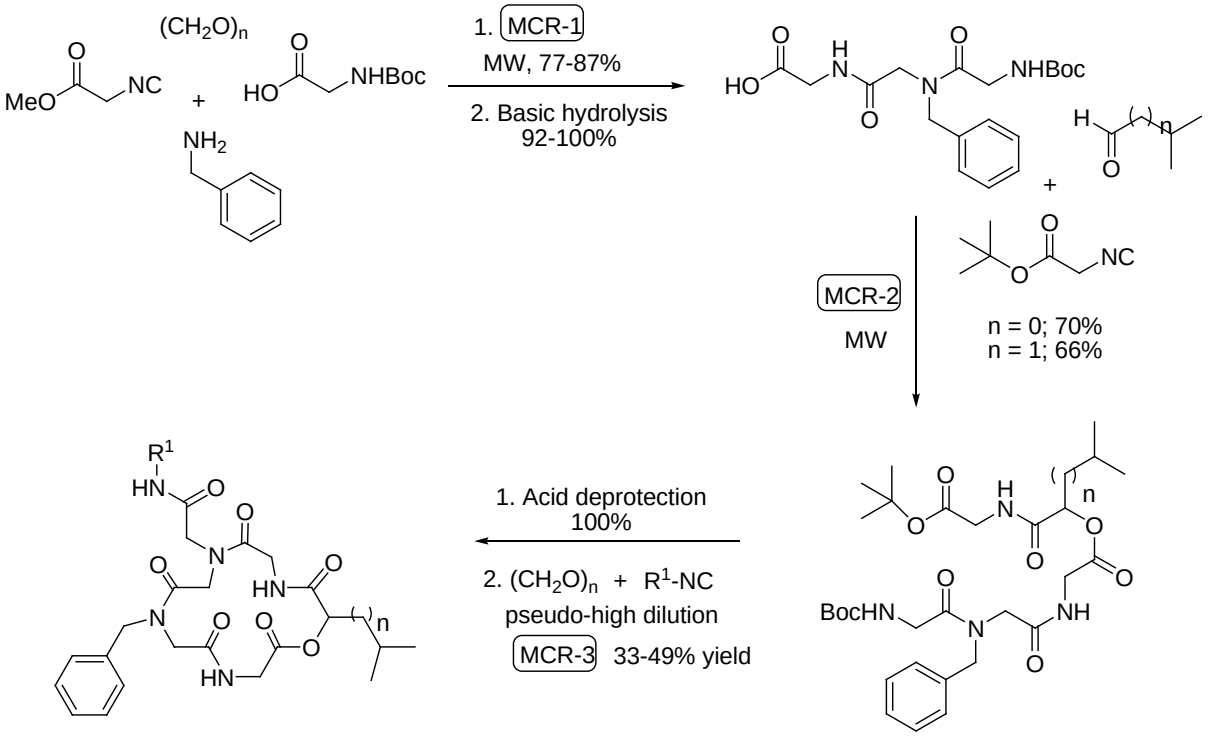
Multicomponent reactions are reactions in which three or more compounds are reacted yielding a product that retains most of the atoms of the starting materials in an atom-economic process. In particular, isocyanide-based multicomponent reactions (IMCRs) are a versatile tool in the synthesis of heterocycles. Among the IMCRs (Passerini and Ugi reactions) the Ugi reaction has been the most used in the consecutive strategy for the synthesis of (macro)heterocycles. This talk will describe recently developed approaches of my research group based on the combination of consecutive isocyanide-based multicomponent reactions for the synthesis of structurally diverse heterocycles.[1] These strategies have also allowed the synthesis of a plethora of macroheterocycles in a reduced number of steps using methyl isocyanoacetate as a versatile isocyanide. An example of this strategy is exemplified in the scheme below.



References:

1 (a) Barreto, A. F. S.; Santos, V. A.; Andrade, C. K. Z. *Beilstein. J. Org. Chem*. **2017**, *13*, 2596. (b) Vercillo, O. E.; Andrade, C. K. Z.; Wessjohann, L. A. *Org. Lett*. **2008**, *10*, 205. (c) Barreto, A. F. S.; Vercillo, O. E.; Birkett, M. A.; Caulfied, J. C.; Wessjohann, L. A.; Andrade, C. K. Z. *Org. Biom. Chem*. **2011**, *9*, 5024. (d) Barreto, A. F. S.; Vercillo, O. E.; Wessjohann, L. A.; Andrade, C. K. Z. *Beilstein J. Org. Chem*. **2014**, *10*, 1017.

MULTICOMPONENT REACTIONS: ADVANCED TOOLS FOR SUSTAINABLE ORGANIC SYNTHESIS

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Multicomponent reactions (MCRs) receive increasing attention because they address both diversity and complexity in organic synthesis. With these one-pot reactions diverse sets of relatively complex structures, especially heterocycles, can be generated from simple starting materials. In many MCRs (e.g. the Ugi reaction), isocyanides are important building blocks. Recently, isocyanides have found also application as versatile C1 building block in palladium catalysis. These reactions offer a vast potential for the synthesis of nitrogen containing fine chemicals. In this presentation, the development of novel atom- and step efficient Pd-catalyzed reactions involving isocyanide insertion will be presented. Further, in order to address stereoselectivity issues connected to certain MCRs, biocatalysis offers unique opportunities. Recently, we have developed several methods based on the enzymatic desymmetrization of meso-pyrrolidines using a monoamine oxidase N (MAO-N) from Aspergillus niger optimized by directed evolution and its combination with highly diastereoselective Ugi-type three-component and Ugi-Smiles reactions. In this presentation we highlight several aspects of this chemistry in the context of heterocycle synthesis with applications in green chemistry and pharmaceuticals.

References:

1 a) G. van Baelen, S. Kuijer, L. Rýček, S. Sergeyev, E. Janssen, F. J. J. de Kanter, B. U. W. Maes, E. Ruijter, R. V. A. Orru, *Chem. Eur. J.* **2011**, *17*, 15039; b) T. Vlaar, E. Ruijter, A. Znabet, E. Janssen, F. J. J. de Kanter, B. U. W. Maes, R. V. A. Orru, *Org. Lett.* **2011**, *13*, 6496; c) T. Vlaar, R. C. Cioc, P. Mampuys, B. U. W. Maes, R. V. A. Orru, E. Ruijter, *Angew. Chem. Int. Ed.* **2012**, *51*, 13058. d) Collet, J.W.; Ackermans, K.; Lambregts, J.; Maes, B.U.W.; Orru, R.V.A.; Ruijter, E. *J. Org. Chem.* **2018**, *83*, 854.

2 a) C. de Graaff, E. Ruijter and R. V. A. Orru, *Chem. Soc. Rev.,* **2012**, *41*, 3969; b) Cioc, RC; Ruijter, E; Orru, RVA, *Green Chemistry* **2014**, *16*, 2958; c) de Graaff, C.; Oppelaar, B.; Péruch, O.; VandeVelde, C.M.L.; Bechi, B.; Turner, N.J.; Ruijter, E.; Orru, R.V.A. *Adv. Synth. Catal.* **2016**, *358*, 1555.

The Ugi reaction in microheterogeneous systems: liposomes, microgels and colloidal crystals

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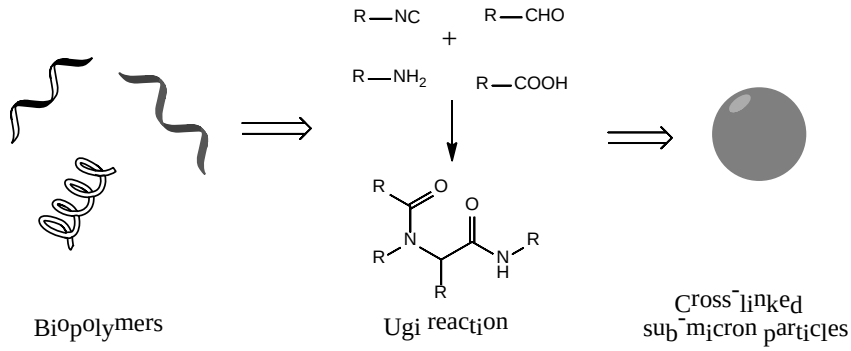
Micro- and nanoparticles developed from biopolymers are preferable over synthetic polymers due to their biocompatibility and have been used for *in vivo* delivery of various pharmaceuticals. Sub-micron particles made from biopolymers can be ideal building blocks for smart materials. However, considerable physical and chemical modifications including crosslinking should be made to improve the poor stability of the biopolymer particles. Our research program is focused on the modification of biopolymers in aqueous suspensions, microemulsions, liposomal, micellar and microgels solutions.[1]

For the preparation of novel biomaterials we explore multi-component reactions (MCRs), which have been highly useful in the modification of polysaccharides. Some MCRs, especially the Ugi reaction, can be accelerated up to 500-fold compared to organic solvents by conducting them in aqueous solutions of polysaccharides. In addition, the Ugi reaction can be applied to modification of practically all types of biopolymers.



This lecture will be focused on the following topics:

1. Acceleration of the Ugi reaction in aqueous solutions of pectin and chitosan.
2. Synthesis of the cross-linked microgels of pectin and cellulose with controlled colloidal properties (average hydrodynamic diameter in the range of 90-360 nm and polydispersity index 0.07-0.15).[2]
3. Method for coating of positively charged liposomal vesicles with modified chitosan and subsequent cross-linking *via* the Ugi reaction.[3]
4. Development of new composite materials based on colloidal crystals and conductive polymers aiming at bio-electronic systems, such as electronic skin. In this case, cellulose microgels form ordered arrays, which include coupled with each other electrically conductive layers.

Obtained materials were tested as effective emulsifiers, novel drug carriers, components of controlled-release systems and a sensitive layer in the electronic skin.

1 M.I. Tokareva, M.N. Ivantsova, M.A. Mironov *Chemistry of Heterocyclic Compounds* **2017***, 53:1,* 2–315.

2 I.D. Shulepov, K.V. Kozhikhova, Y.O. Panfilova, M.N. Ivantsova, M.A. Mironov *Cellulose* **2016**, *23*, 2549–2559.

3 K.V. Kozhikhova, M.N. Ivantsova, M.I. Tokareva, I.D. Shulepov, A.V. Tretiyakov, L.V. Shaidarov, V.L. Rusinov, M.A. Mironov Pharmaceutical Development and Technology, **2018**, *23:4*, 334-342.

Three-Component Reactions of Alkoxyallenes, Nitriles and Carboxylic Acids New Routes to Highly Functionalized Heterocycles

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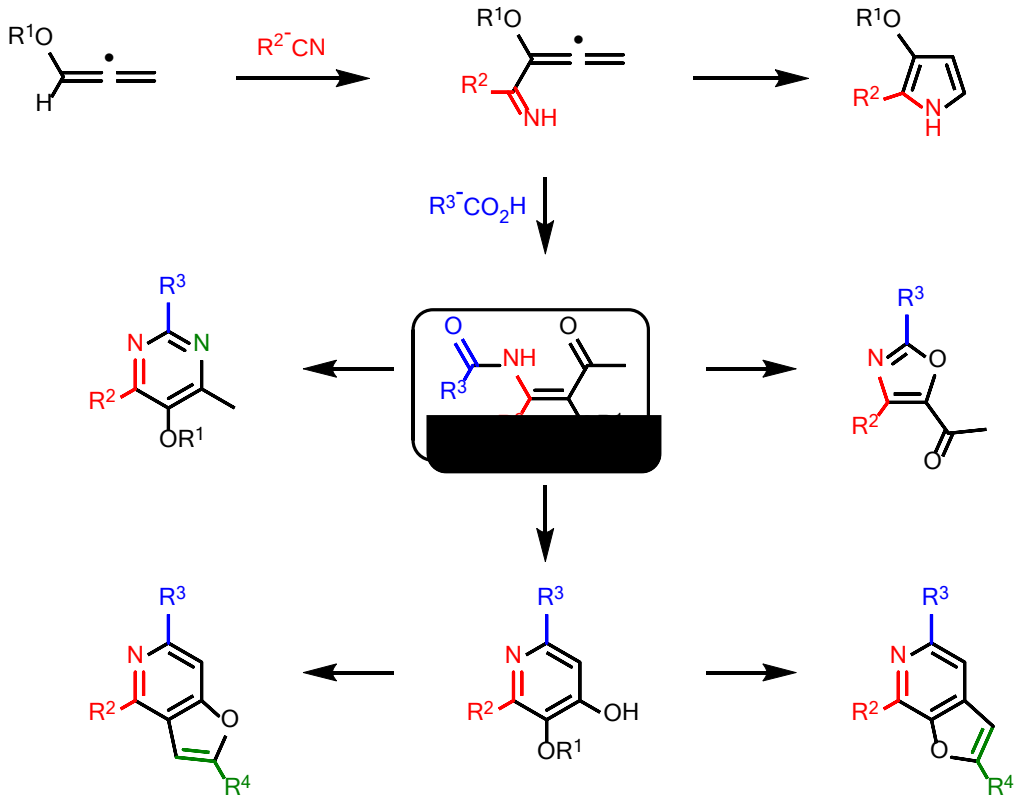
A serendipitously discovered three-component reaction of lithiated alkoxyallenes, nitriles and carboxylic acids provides β-ketoenamides that are used for the synthesis of highly functionalized pyrimidines, oxazoles and pyridines.[1] The functional groups of the products can be employed for further transformations, in particular palladium-catalyzed reactions, leading to a large collection of interesting (poly)heterocyclic systems.[2]



Acknowledgements: This work was supported by the Deutsche Forschungsgemeinschaft, the Alexander von Humboldt-Stiftung, the Fonds der Chemischen Industrie and Bayer HealthCare AG.

References:

1. Discovery: a) O. Flögel, J. Dash, I. Brüdgam, H. Hartl, H.-U. Reissig, *Chem. Eur. J.* **2004**, *10*, 4283. b) J. Dash, T. Lechel, H.-U. Reissig, *Org. Lett.* **2007**, *9*, 5541.

2. Reviews: a) M. Brasholz, H.-U. Reissig, R. Zimmer, *Acc. Chem. Res.* **2009**, *42*, 45. b) T. Lechel, H.-U. Reissig, *Pure Appl. Chem.* **2010**, *82*, 1835. c) T. Lechel, H.-U. Reissig, in *Targets in Heterocyclic Chemistry* **2016**, *20*, 1.

Activated Alkynes in Domino and Multicomponent Reactions with Azaheterocycles towards Molecular Complexity

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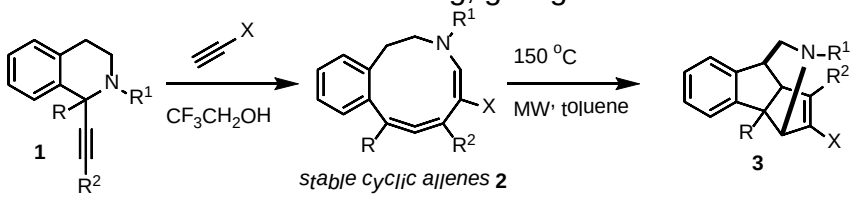
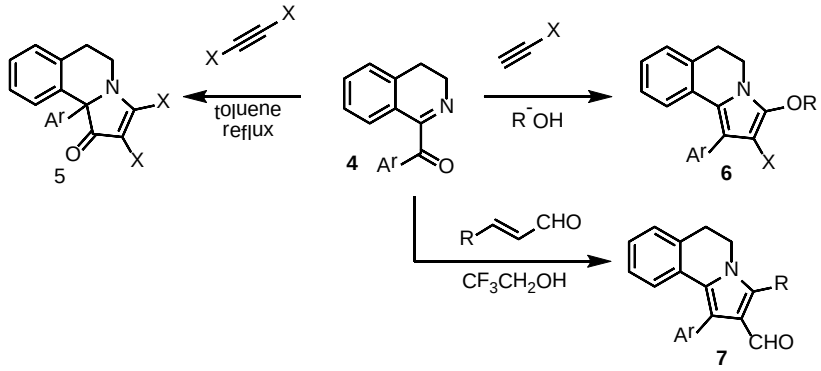
Alkynes, bearing electron-withdrawal groups, are well-recognized reagents in organic synthesis, especially for heterocyclic preparation and generating molecular complexity. Capable for diverse transformations, activated alkynes found broad use in reactions with saturated azaheterocycles, giving 8-, 9- and 10-membered rings as a result of ring expansion. We have recently found that the interaction of 1-alkynyl-substituted tetrahydroisoquinolines **1** with activated alkynes leads to the formation of an unusual class of cyclic allenes **2** [1], stable under standard conditions, but ready to undergo further transformations on heating, giving intrinsic architectures **3**.



Our interest in chemistry of activated alkynes resulted in a series of syntheses towards pyrrolo[2,1-*a*]isoquinoline scaffold, incorporated in *Lamellarine* alkaloid family, showing the possibility to convert 1-aroyl-3,4-dihydroisoquinolines **4** into 1-oxo-derivatives **5** [2] or alkoxypyrroloisoquinoline compounds **6** [3]. We have also demonstrated the possibility to use unsaturated alkene exemplified by acrolein in analogous transformations to give products **7** [4]. Further studies in the field are concerning reactivity of highly interesting imidazolidines under the action of activated alkynes.



Reference

1. L.G. Voskressensky *et al New J. Chem.*, **2017**, *41*, 1902-1904
2. L.G. Voskressensky *et al Tetrahedron Lett.*, **2017**, *58*, 877-879
3. L.G. Voskressensky *et al RSC Advances*, **2016**, *6*, 74068-74071
4. L.G. Voskressensky *et al Synthesis*, **2017**, *49*, 5251-5257

The work was prepared with the support of the "RUDN University Program 5-100"

Visible-Light Mediated Three-Component Synthesis of Sulfones and Aminosulfonamides from Sulfur Dioxide

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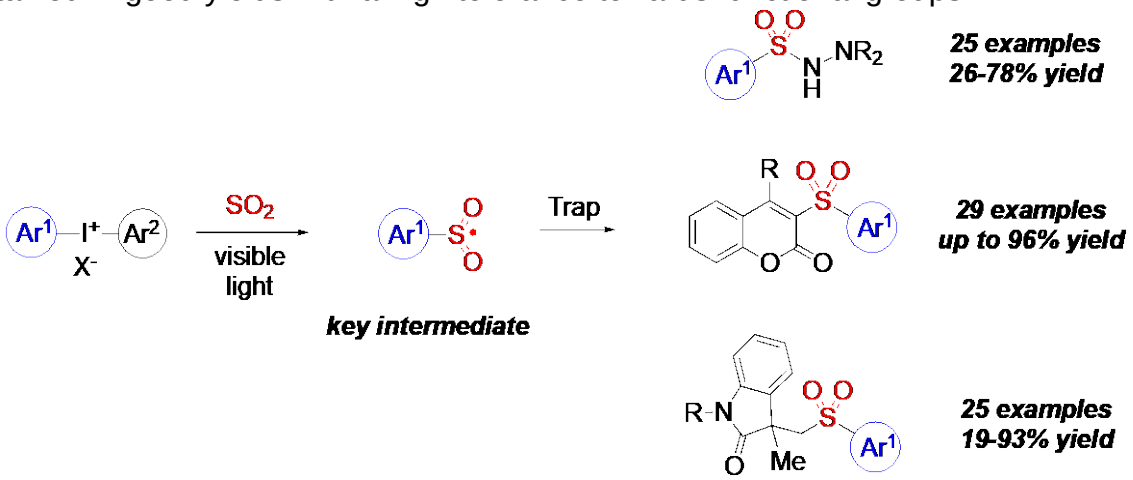
Molecules containing a sulfonyl-dervied (-SO_2-) functional group, such as sulfones or sulfonamides, play an important role in organic chemistry and have found widespread application, in particular in medicinal chemistry. In the last years, novel methods for the based on sulfur dioxide as key building block have become an attractive approach for the construction of the sulfonyl moiety.[1] In this context, radical-based transformations with sulfur dioxide have emerged as a versatile tool for the synthesis of molecules containing a sulfonyl functionality.[2]

Herein, novel methods for the multicomponent synthesis of sulfones and aminosulfonamides using sulfur dioxide as central building block are presented. These reactions are based on the visible-light mediated generation of aryl radicals using diaryliodonium salts as radical precursors. In the presence of sulfur dioxide or a suitable surrogate, aryl sulfonyl radicals are formed, which can be captured with suitable trapping agents. The reactivity of the aryl sulfonyl radicals could be harnessed for the construction of aminosulfonamides[3a] as well as for the synthesis of sulfonylated coumarins[3b] and oxindoles.[3c] In all cases, the desired products were obtained in good yields with a high tolerance towards functional groups.



In summary, these reactions enable the construction of molecules containing a sulfonyl group using sulfur dioxide as key building block and visible light as driving force. Such processes can open new exiting opportunities for the sustainable synthesis of sulfones and sulfonamides via visible-light mediated fixation of sulfur dioxide.

References:

1 a) M. Feng, B. Tang, S. H. Liang, X. Jiang, *Curr. Top. Med. Chem.* **2016**, *16*, 1200; b) E. J. Emmet, M. C. Willis, *Asian J. Org. Chem.* **2015**, *4*, 602.

2 K. Hofman, N.-W. Liu, G. Manolikakes, *Chem. Eur. J.* **2018**, *available online*, DOI: 10.1002/chem.201705470.

3 a) N.-W. Liu, S. Liang, G. Manolikakes, *Adv. Synth. Catal.* **2017**, *359*, 4117; b) Z. Chen, N.-W. Liu, M. Bolte H. Ren, G. Manolikakes, *Green Chemistry* **2018**, *20*, 3059; c) N.-W. Liu, Z. Chen, A. Herbert, H. Ren, G. Manolikakes, *manuscript submitted*.

From natural amino acids to bifunctional chiral isocyanides

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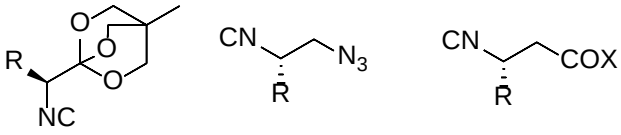
Ugi and Passerini reactions are most efficient way to molecular complexity. They open access to peptides and depsipeptides bearing the α-amino acid and α-hydroxy acid moiety in only one synthetic step using isocyanides as a key building blocks. Out of four or three imputs of this multicomponent reactions isocyanides are most important reagents. On the other hand family of these unique compounds is very limited. Using natural amino acids we elaborated efficient synthesis of some polifunctional isocyanides and demonstrated their high synthetic utility (Scheme 1). For example, a family of nonracemizable isocyanoacetic acid derivatives, azido substituted isocyanides and β_3-isocyanopropionates was elaborated.



X= OR, NHR,
amino acid residue

Scheme 1.

Combination of the two "worlds" chemo- and biocatalysis toward multi-step one-pot processes

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Multi-step one-pot processes represent an attractive synthetic concept for the improvement of overall process efficiency by decreasing the required number of work up and purification steps. By avoiding such time-, capacity- and solvent-intensive process steps, multi-step one-pot syntheses contribute to a significantly improved process economy as well as to more sustainable synthetic routes. A key criterion for multi-step one-pot processes is the compatibility of the individual reaction steps with each other. Accordingly, most of today´s known multi-step one-pot processes are based on either chemocatalytic multi-step reactions or "pure" biotechnological processes such as, e.g., fermentation. In contrast, successful combinations of chemo- and biocatalytic reactions, in particular in aqueous reaction media, are much less widely known.[1]

In this contribution strategies for the combination of chemo- and biocatalysts towards the development of multi-step one-pot processes in aqueous reaction media are presented. Since palladium-catalyzed cross-coupling reactions are of particular importance in the field of metal catalysis, as enzymatic reductions are in the field of biocatalysis, we were interested in the investigation of the compatibility of these types of reactions with each other in water. As an example for such a one-pot process the synthesis of chiral biaryl-containing alcohols via Suzuki-cross-coupling reaction and subsequent asymmetric enzymatic reduction is shown.[2] A further research focus has been on the combination of enzyme-compatible organocatalytic reactions with biotransformations. It turned out that a reaction mixture resulting from an asymmetric organocatalytic aldol reaction is compatible with a direct subsequent enzymatic reduction without the need for a work-up step of the aldol reaction.[3,4] In addition, an organocatalytic nitroalkene synthesis has been successfully combined with its subsequent ene reductase-catalyzed asymmetric reduction, leading to the corresponding nitroalkane with high enantioselectivity.[5]

When utilizing catalysts, which strongly differ in their "process windows", conditions for compatibility and a combined use in the same reaction environment might not be reached. In these cases, however, compartmentalization might represent a solution for combining them in a cascade process running in one reactor. Such a compartmentalization approach for a one-pot process was demonstrated, e.g., for the combination of a palladium-catalyzed Wacker-oxidation with an alcohol dehydrogenase-catalyzed ketone reduction.[6]

References:

1 F. Rudroff, M. D. Mihovilovic, H. Gröger, R. Snajdrova, H. Iding, U.T. Bornscheuer, *Nature Catal.* **2018**, *1*, 12.
2 E. Burda, W. Hummel, H. Gröger, *Angew. Chem. Int. Ed.* **2008**, *47*, 9551.
3 K. Baer, M. Kraußer, E. Burda, W. Hummel, A. Berkessel, H. Gröger, *Angew. Chem. Int. Ed.* **2009**, *48*, 9355.
4 G. Rulli, N. Duangdee, K. Baer, W. Hummel, A. Berkessel, H. Gröger, *Angew. Chem. Int. Ed*. **2011**, *50*, 7944.
5 E. Burda, T. Ress, T. Winkler, C. Giese, X. Kostrov, T. Huber, W. Hummel, H. Gröger, *Angew. Chem. Int. Ed.* **2013**, 52, 9323.
6 H. Sato, W. Hummel, H. Gröger, *Angew. Chem. Int. Ed*. **2015**, *54*, 4488.

Novel NHC-Mediated, Multicatalytic MCR Transformations

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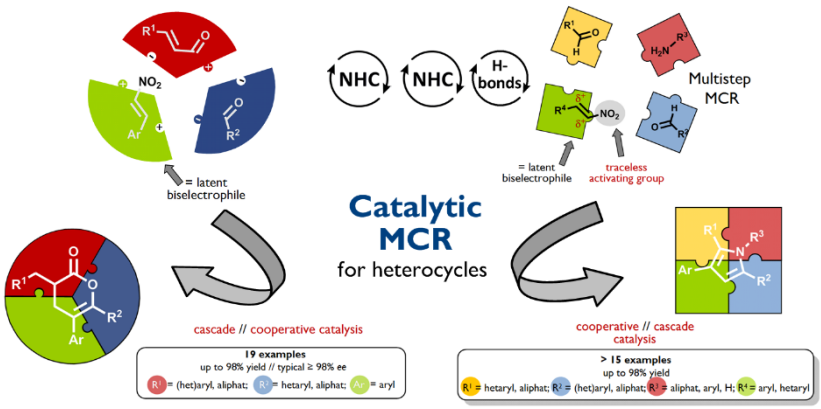
Catalysis undoubtedly is recognized as a key methodology in organic chemistry allowing for efficient and sustainable synthetic procedures; its implementation in multicomponent reactions (MCRs) is both challenging, but also offers great possiblities for unprecedented transformations proceeding with high efficiency.

While the efficiency of processes achieved in nature is still unmet, newly developed synthetic methodology often relies on biomimetic principles and insights how to enable formerly unattainable bond construction. This for example includes umpolung processes[1,2] as known from thiamine dependent enzymes. *N*-heterocyclic carbene (NHC) catalysis adapts this “blueprint” for the development of novel synthetic strategies and methodology.

Multicatalytic processes, where more than one reaction partner experiences activation, allowing for their successive (domino and cascade catalysis) or concurrent transformation (synergistic and cooperative catalysis) into reactive intermediates are among such interesting strategies. Especially orthogonal activation *via* umpolung in the context of sequential one-pot transformations offers fast access to complex, multifunctional products from simple, easily available starting material.[3,4,5]



This lecture will describe our latest advances in developing both novel NHC catalyzed new (multi)catalytic, multicomponent reactions.

References:

1 a) K. Zeitler, *Angew. Chem. Int. Ed.* **2005**, *44*, 7506; b) D. M. Flanigan, F. Romanov-Michailidis, N. A. White, T. Rovis, *Chem. Rev.* **2015**, *115*, 9307.

2 C. A. Rose, S. Gundala, C.-L. Fagan, S. J. Connon, J. F. Franz, K. Zeitler, *Chem. Sci.* **2012**, *3*, 735.

3 J. F. Franz, P. J. W. Fuchs, K. Zeitler, *Tetrahedron Lett.* **2011**, *52*, 6952.

4. P. J. W. Fuchs, K. Zeitler, *J. Org. Chem.* **2017**, *82,* 7796.

5. P. J. W. Fuchs, K. Zeitler, *Org. Lett.* **2017**, *19,* 6076.

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Multicomponent Polymerizations of Alkyne for Functional Polymer Synthesis

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The development of new polymerizations inspired from organic frontier is crucial for the exploration of new polymer materials. Multicomponent polymerizations (MCPs), which inherited the advantages of multicomponent reactions such as great structural diversity, high efficiency, atom economy, and various combination of reactants, has become a promising tool for the construction of functional polymers. However, the reported products of MCPs are limited, which generally include polyesters, polyamides, and polyamines with relatively simple structures.

To expand the applicability of multicomponent polymerizations and enrich product structures, the one-pot two-step multicomponent tandem polymerizations (MCTPs) of alkynes are proposed for the synthesis of conjugated polymer products. Through such strategy, side reactions are inhibited to ensure high efficiency and product specificity, and a great diversity of reactions can be applied. Polyheterocycles with well-defined and sequence-controlled structures can also be obtained through metal-free MCTPs. Moreover, through MCTP, polymer main chain structure, chemical structure, as well as sequence structure can be controlled, and unconventional luminescent polymers without extensive conjugation can be obtained. Furthermore, simple monomers such as elemental sulfur can be directly used for multicomponent polymerization to generate functional polymers, demonstrating high economic efficiency. These MCPs not only connect functional units together in polymer chain, but also directly construct multiple types of covalent bonds and new functional units, showing great synthetic efficiency. To conclude, the MCPs of alkyne enjoy high synthetic and economic efficiency, good controllability and practicability, which is anticipated to promote the development of advanced functional polymers.

References:

1 T. Tian, R. Hu, B. Z. Tang, *J. Am. Chem. Soc*. **2018**, DOI: 10.1021/jacs.8b02886.
2 B. Wei, W. Li, Z. Zhao, A. Qin, R. Hu, B. Z. Tang, *J. Am. Chem. Soc*. **2017**, *139*, 5075.
3 X. Tang, C. Zheng, Y. Chen, Z. Zhao, A. Qin, R. Hu, B. Z. Tang, *Macromolecules* **2016**, *49*, 9291.
4 W. Li, X. Wu, Z. Zhao, A. Qin, R. Hu, B. Z. Tang, *Macromolecules* **2015**, *48*, 7747.

Multicomponent reactions in polymer science: from versatile tuning of structure and properties to sequence defined macromolecules

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Multicomponent reactions are an established tool in organic chemistry. They offer high atom-economy, straightforward practical procedures and most importantly structural diversity can easily be achieved by variation of the used components. Only recently, the benefit of these one-pot reactions was realized for macromolecular engineering. Especially the Passerini three-component (P-3CR) and Ugi four-component (U-4CR) reactions demonstrate attractive tools for polymer synthesis.[1] Several approaches will be discussed, focusing on the preparation of highly defined polymeric architectures. For instance, star-shaped block copolymers were prepared via multicomponent step-growth polymerization[2] and subsequently modified with PEG to obtain water soluble unimolecular micelles that show an interesting encapsulation property (Figure 1).[3] Moreover, multicomponent reactions are an excellent tool for the design of monodisperse macromolecules, including sequence defined polymers,[4,5] also in combination with other methods of sequence definition.[6] Their synthesis and first applications for data storage and transportation will be highlighted.

Figure 1: Encapsulation of guest molecule by a star-shaped block copolymer prepared via the P-3CR.[3]

References:

[1] A. Sehlinger, M. A. R. Meier, *Prog. Polym. Sci.* **2015**, 269, 61-86.
[2] S. Oelmann, S. C. Solleder, M. A. R. Meier, *Polym. Chem.* **2016**, *7*, 1857-1860.
[3] S. Oelmann, M. A. R. Meier, *RSC Adv.* **2017**, *7*, 45195-45199.
[4] S. C. Solleder, M. A. R. Meier, *Angew. Chem. Int. Ed.* **2014**, *53*, 711-714.
[5] S. C. Solleder, D. Zengel, K. S. Wetzel, M. A. R. Meier, *Angew. Chem. Int. Ed.* **2016**, *55*, 1204-1207.
[6] S. C. Solleder, S. Martens, P. Espel, F. Du Prez, M. A. R. Meier, *Chem. Eur. J.* **2017**, *23*, 13906.

Short Lectures

Drug discovery at the speed of sound

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A blockbuster drug generates > $ 1 billion revenues per year. Each day not on the market corresponds to a loss of > $ 2.7 million. Multiple benchmark reports suggest development costs of drugs are skyrocketing while the introduction of novel drugs is decreasing or at best stagnating. Part of the problems can be attributed to the preclinical drug discovery and development involving expensive high throughput screening (HTS) and hit-to-lead campaigns using mostly traditional technologies.
Here we introduce a fundamentally novel approach towards preclinical drug discovery and development by blending Instant Chemistry, nL dispensing, acoustic-MS, uHTS and artificial intelligence.
Acoustic droplet ejection (ADE) technology allows for the fast, contact-less and accurate transfer of very small droplets (nL) from plate to plate of different high density formats. ADE has had a dramatic impact in different technology areas, including drug discovery, cancer research and genomic research and is used in many laboratories world-wide. However, ADE has never been used in miniaturization and acceleration of library synthesis for uHT to dramatically accelerate the preclinical drug discovery cycle.
One-pot multicomponent reactions (Instant Chemistry, MCRs) are suitable to create very large libraries of small molecules and macrocycles [1-2]. A prototype instrumentation platform is developed which allows for the parallel synthesis of hundreds of libraries of scaffolds on an unprecedented dense format. The platform is integrated with acoustic-MS for quality control and an efficient affinity-based mass-spectrometry screening platform using the same high-density format. Artificial intelligence is developed to ensure never-seen-before fast cycle times for hit-2-lead progression [3].
We applied speed of sound technology successfully to different protein-protein interactions including menin-MLL, p53-MDM2 and IL17.
References:
[1] A. Domling, W. Wang, K. Wang, *Chem. Rev.* **2012**, *112*, 3083-3135.
[2] R. Madharvachary et al., *Angew. Chem. Intl. Ed. Engl.* **2017**, *56*, 10725-10729.
[3] L. Weber et al., *Angew. Chem. Intl. Ed. Engl.* **1995**, *34*, 1521-3773.

Ugi's Legacy: From Multicomponent Reactions to Natural Product Synthesis

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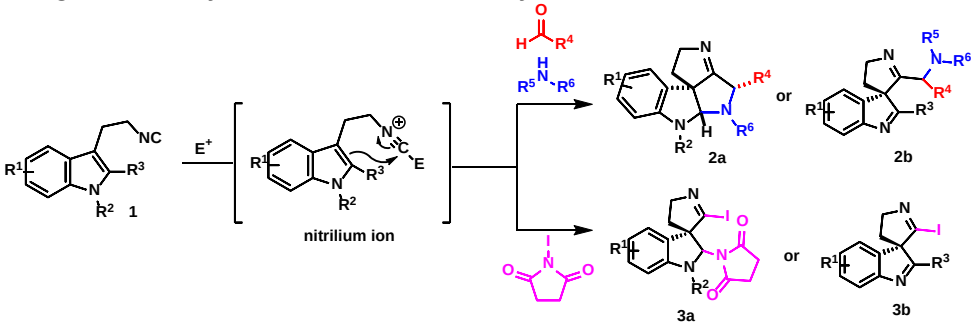
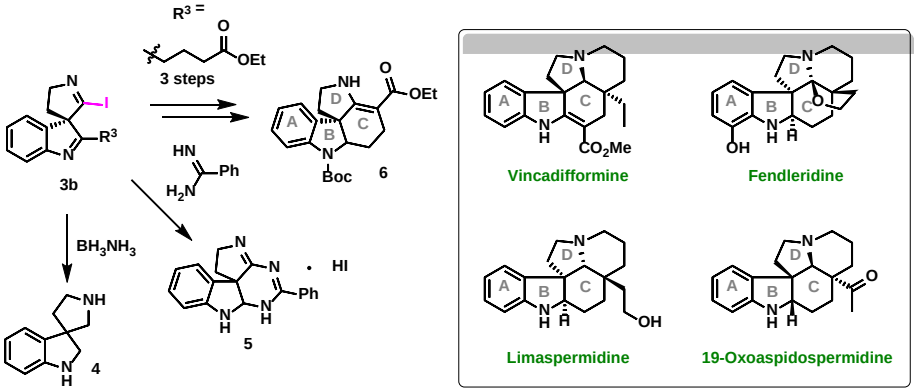
Isocyanide-based multicomponent reactions (IMCRs) have been widely accepted as a robust tool to quickly generate highly functionalized architectures. Although the classical Passerini[1] and Ugi[2] reactions have been extensively investigated, research is still ongoing to explore reaction pathways that differ from the traditional reaction mechanisms. The nitrilium ion intermediate plays a crucial role in the design of many of these novel transformations. A common strategy is to tether a nucleophile to one of the components to generate a range of heterocycles.[3] We have exploited this concept by using tryptamine-derived isocyanides (**1**) in Ugi-type reactions to generate tri- and tetracyclic spiroindolines (**2**).[4] In addition, isocyanides **1** are suitable reaction partners with halogenating agents. Reaction with *N*-iodosuccinimide (NIS) afford a surprisingly stable imidoyl iodide (**3**), which offers significant opportunities for the synthesis of complex indoline heterocycles and natural products (Scheme 2). Herein we will discuss the remarkable chemistry of tryptamine-derived isocyanides, going from Ugi chemistry to more exotic iodocyclization reactions.



Scheme 1. Two isocyanide-based spirocyclization approaches with tryptamine derived isocyanides



Scheme 2. Imidoyl iodide 3b as a valuable building block in the synthesis of indoline heterocycles and natural products

References

(1) Passerini, M.; Simone, L. *Gazz. Chim. Ital.* **1921**, *51*, 126.
(2) Ugi, I.; Steinbrückner, C. *Chem. Ber.* **1961**, *94*, 734.
(3) Váradi, A.; Palmer, T.; Dardashti, R. N.; Majumdar, S. *Molecules* **2015**, *21*, 19.
(4) Saya, J. M.; Oppelaar, B.; Cioc, R. C.; van der Heijden, G.; Vande Velde, C. M. L.; Orru, R. V. A.; Ruijter, E. *Chem. Commun.* **2016**, *52*, 12482.

Selective Groebke-Blackburn-Bienaymé Reactions for Modification of Drugs with Diaminodiazine Cores.

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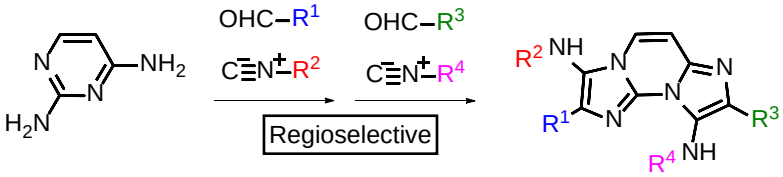
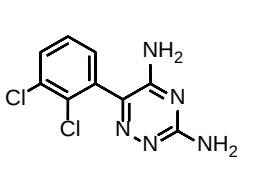
Aminoimidazoles, relevant scaffolds in medicinal chemistry,[1] can be assembled by the condensation of aldehydes, isocyanides and α-amino azines through Groebke-Blackburn-Bienaymé reaction (GBBR). Our group has recently discovered "selective multiple GBBRs", yielding N-fused polyheterocyclic scaffolds. The liability, regioselectivity and broad scope of these transformations, could be exploited to generate screening libraries for medical applications.

Multiple GBBRs:

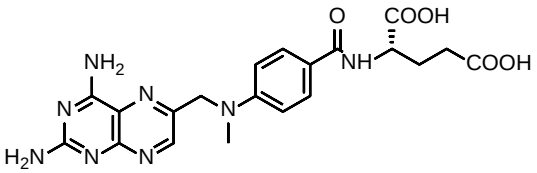


Trimethoprim (antibiotic), methotrexate (chemotherapy agent) and lamotrigine (anticonvulsant), present in the World Health Organization's List of Essential Medicines, are examples of commercial drugs with the diaminopyrimidine motif. Their diaminodiazine cores can elaborated through selective multiple GBBRs. The novel scaffolds can be decorated with up to four diversity points to access more efficient analogues.

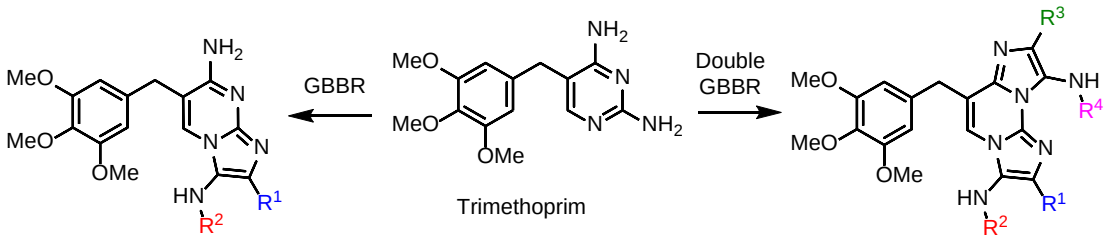
Trimethoprim (TMP) is commonly prescribed for the treatment of a variety of microbial infections in animals and human. However, despite its efficiency, TMP-resistance is a frequently reported issue.[2] Therefore, facilitated access to structurally tunable analogues is utterly important. In this regard, a set of TMP analougues were synthesized through our multiple GBBR procedure, using a variety of aldehydes and isocyanides. The bioactivity of these compounds has been determined. Studies to synthesize a set of lamotrigine analogues are ongoing.



Lamotrigine



Methotrexate



References:
1 N. Devi, R.K. Rawal, V. Singh, *Tetrahedron* **2015**, *71*, 183. And references cited therein.
2 P. Huovinen, L. Sundström, G. Swedberg, O. Sköld, *Antimicrob. Agents Chemother*. **1995**, *39*, 279.

Synthesis of Polyheterocycles *via* Multicomponent Reactions

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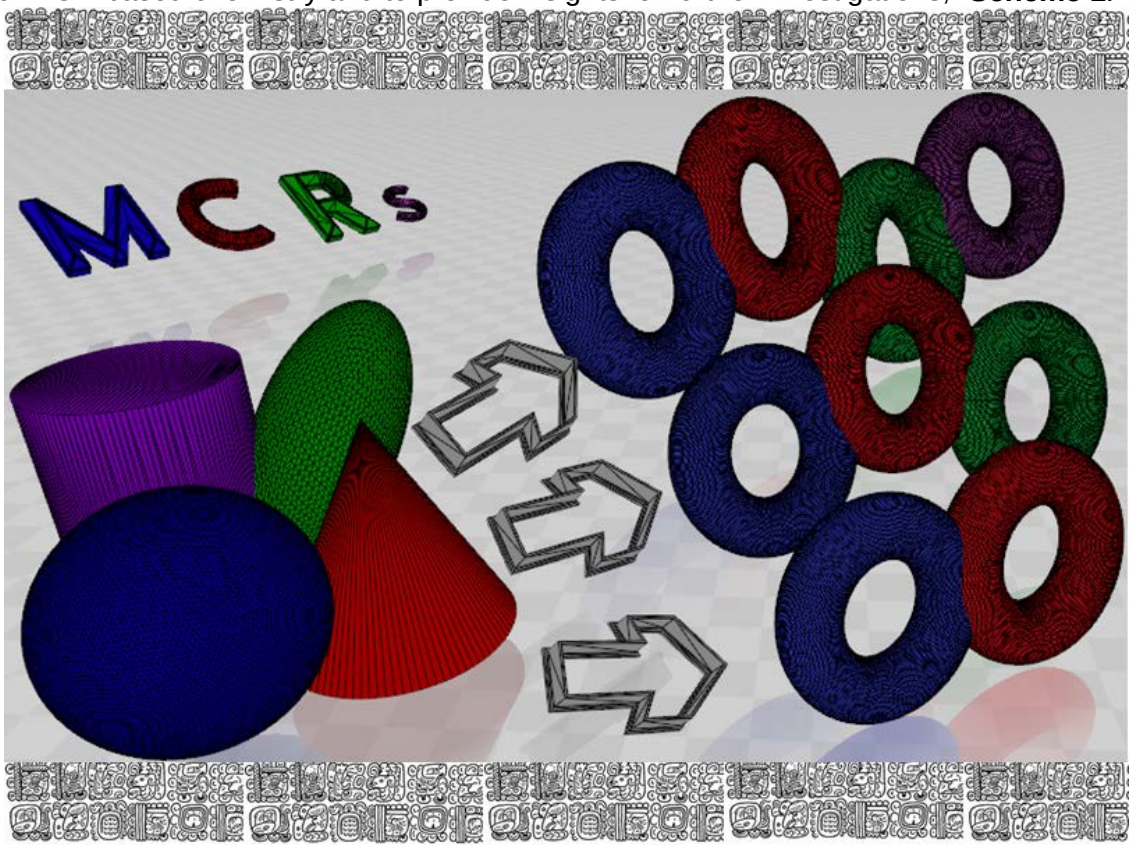
Polyheterocycles are one of the most wanted synthetic targets due to their numerous and valuable applications in various fields of knowledge like agrochemistry, materials and polymers science, dyes and pigments science, optics and more important, in medicinal chemistry. Multicomponent reactions (MCR's) are highly convergent one pot processes, in which at least three reagents are combined sequentially to assemble complex molecules containing almost all atoms coming from the starting materials. In this context, the synthesis of 'heterocycles' via MCR's-based processes has often been reviewed. However, there was not a review (recent or otherwise) covering the synthesis of 'polyheterocycles' via direct MCR's, nor one pot processes involving MCR's coupled to further cyclizations (via ionic, metal-catalyzed, pericyclic, or free-radical-mediated cyclizations). Thus, we want to present our most recent review covering this important issue, which categorizes the key processes involved in the syntheses of polyheterocycles, aiming to give readers an easy understanding of MCR-based chemistry and to provide insights for further investigations,[1] **Scheme 1**.



Scheme 1. Synthesis of Polyheterocycles *via* Multicomponent Reactions (FRONT COVER OF THE ISSUE taken from *Org. & Biomol. Chem.* **2018**, *16*, 1402)

References:

1 I.A. Ibarra, A. Islas-Jácome, E. González-Zamora. *Org. Biomol. Chem.* **2018**, *16*, 1402. (DOI: 10.1039/c7ob02305g)

Biginelli Reaction Enabled the Discovery and SAR Exploration of Novel Potent and Selective A_{2B} Antagonist Chemotypes

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A_{2B} receptor antagonists constitute an emerging family of therapeutics promising the development of conceptually novel approaches for the treatment of diabetes, asthma, chronic obstructive pulmonary disease or cancer.[1] We recently described a novel family of potent and selective non-xanthine A_{2B} antagonists [e.g. 3,4-dihydropyrimidin-2(1*H*)-ones] by the using the highly reliable Biginelli reaction.[2,3] Using a scaffold hoping approach and exploiting the diversity of 1,3-dinucleophiles that can be employed in the three component Biginelli reaction, we herein document the discovery of novel highly potent A_{2B} antagonist chemotypes as well as the structure-activity relationship in these series.

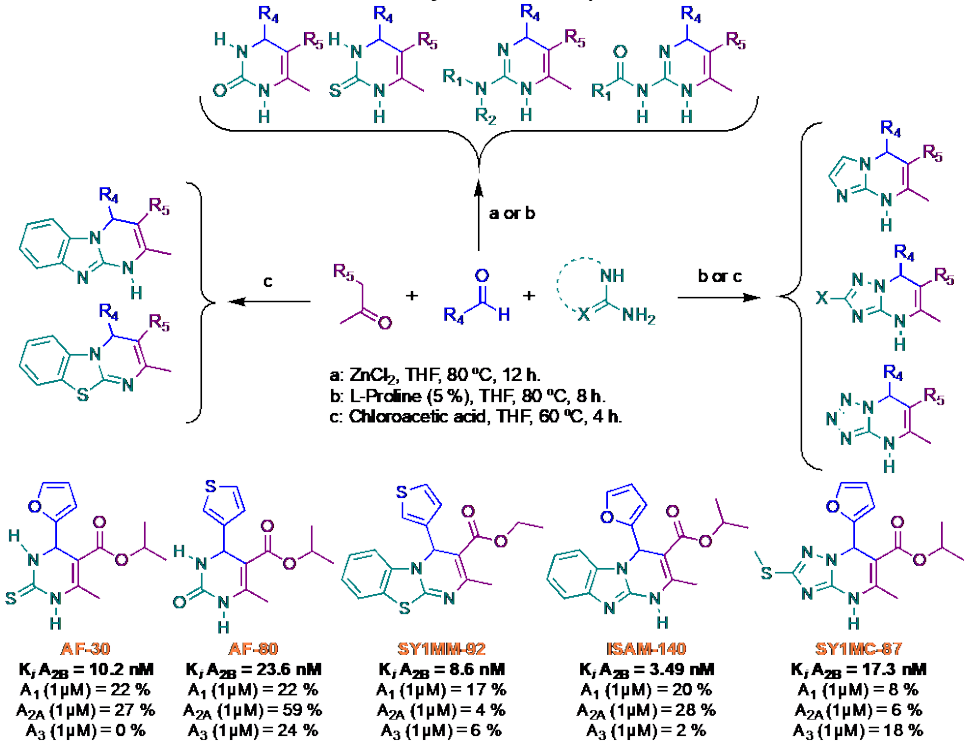

Figure 1. Synthetic scheme employed for library synthesis and biological data of some lead compounds.

References:

1 Müller, C. E. Jacobson, A. J. *Biochim. Biophys. Acta* **2011**, *1808*, 1290.

2 Crespo, A. El Maatougui, A. Biagini, P. Azuaje, J. Brea, J. Loza, M. I. Cadavid, M. I. García-Mera, X. Gutiérrez-de-Terán, H. Sotelo, E. *ACS Med. Chem. Lett*. **2013**, *4*, 1031.

3 El Maatougui, A., Azuaje, J., Gonzaĺez-Gomez, M., Miguez, G., Crespo, A., Carbajales, C., Escalante, L., García-Mera, X., Gutieŕrez-de-Terań, H., Sotelo, E., *J. Med. Chem*. **2016**, *59*, 1967.

Synthesis of Functionalized Heterocyclic Skeletons through Novel 3-Formyl Chromone Based Multicomponent Reactions

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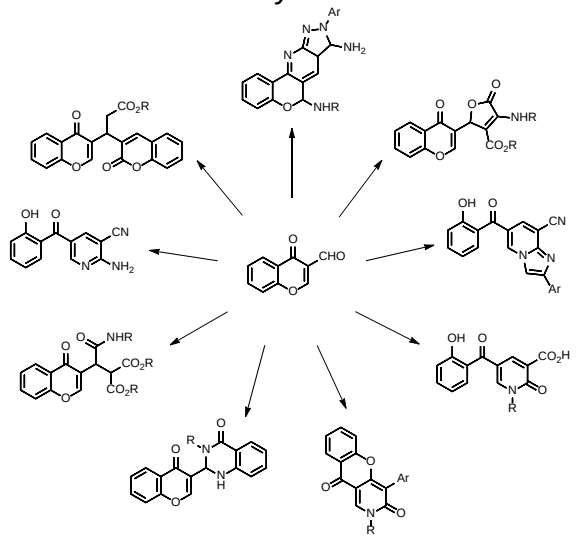
The synthesis of new chemical structures has always been a major challenge in the field of organic synthesis. In this context, multicomponent reactions (MCRs) are a powerful synthetic approach for generating complex molecules and are suitable for exploring substituent diversity.

3-Formyl chromones are used for the construction of different heterocyclic systems through reactions with binucleophiles. Meanwhile, chromonyl Meldrum's acid is suitable substrate as starting material as a source of the chromone scaffold for its insertion into the structure of biologically active compounds.

Here, we present different multicomponent reactions based on 3-formyl chromone and chromonyl Meldrum's acid that could be used for the synthesis of different heterocyclic skeletons through the ring opening of chromone or without ring opening and formation of the functionalized chromone. For example, synthesis of chromone hydrazide and its reaction with malononitrile and primary amines in the presence of trimethylamine leading to fused pyrazolopyridines with chromone moiety.

This presentation will focus on the synthesis of chromone derivatives and using them for the synthesis of functionalized heterocyclic skeletons.



References:

1. Plaskon, A.S.; Grygorenko, O.O.; Ryabukhin, S.V. *Tetrahedron*, **2012**, *68*, 2743.
2. a)Balalaie, S.; Derakhshanpanah, F. ; Zolfigol, M.A.; Rominger, F. *Synlett*, **2018**, 89; b)Balalaie, S.; Bijanzadeh, H.R.; Mehrparvar, S.; Rominger, F. *Synlett*, **2016**, 782; c) Balalaie, S.; Navari, R.; Nibakht, A. ; Hamdan, F.; Mirzaie, S.; Rominger, F. Submitted for publication.

LA-catalyzed divergent reactions between 3-diazo-indolin-2-imines and aryl aldehydes

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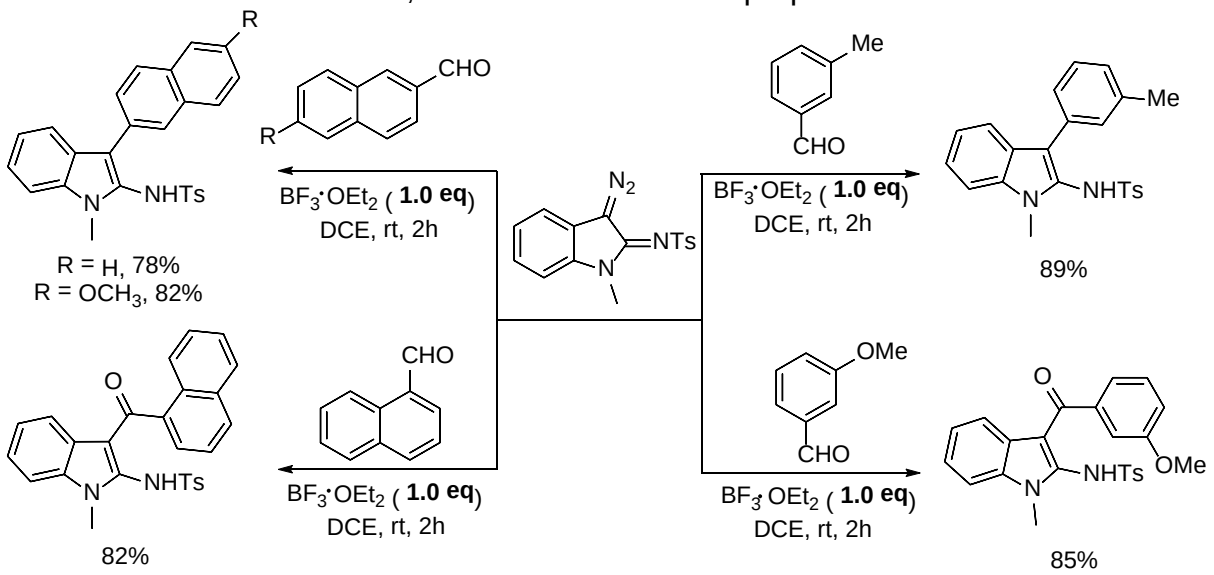
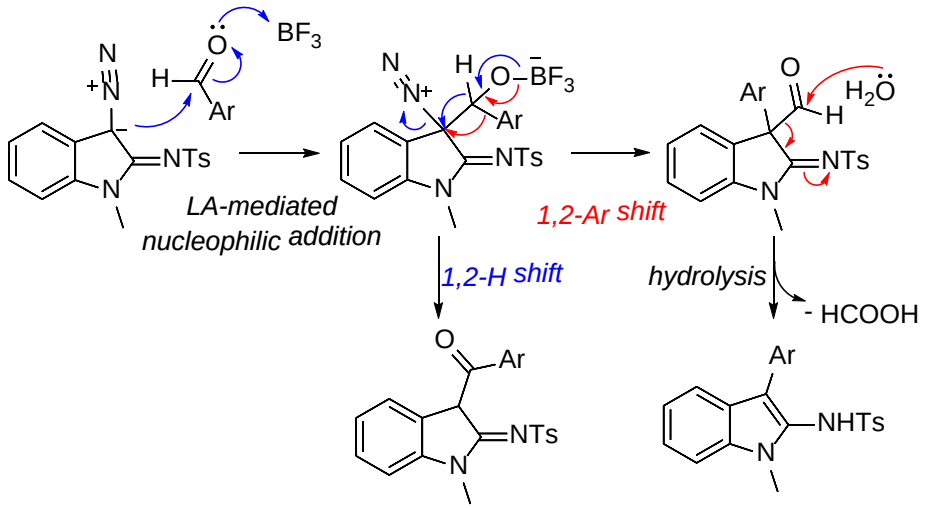
Compounds containing indole skeleton are important in both life science, especially to those with aryl or acyl groups on 3-position of indole.[1] In this work, a Lewis acid catalyzed reaction between 3-diazo-indolin-2-imines[2] and aryl aldehydes was reported. The reaction outcome depended on the structure of aryl aldehydes as illustrated by the typical examples listed in Scheme 1. In order to understand this substrate-controlled reaction, the mechanisms were proposed in Scheme 2.



Scheme 1 Substrate-controlled reaction between 3-diazo-indolin-2-imines and aldehydes



Scheme 2 Proposed mechanisms for the selective formation of products

References:

1 S. Hibino, T. Choshi, *Nat. Prod. Rep.* **2002**, *19*, 148.
2 (a) Y. Xing, G. Sheng, J. Wang, P. Lu, Y. Wang, *Org. Lett.* **2014**, *16*, 1244; (b) G. Sheng, K. Huang, Z. Chi, H. Ding, Y. Xing, P. Lu, Y. Wang, *Org. Lett*. **2014**, *16*, 5096.

Homophtalonitrile as a valuable reagent for multicomponent reactions

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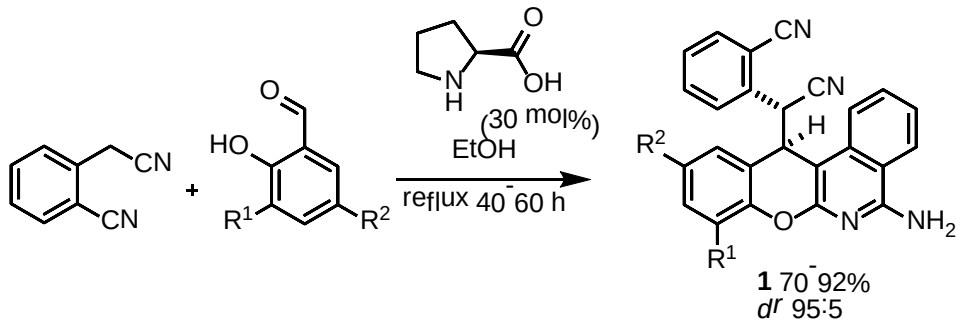
Nitrile compounds, especially dinitriles, found great relevance in the field of domino and multicomponent reactions. Thus, reactions of malondinitrile are well known and studied, and usually produce 2-aminochromenes, a privileged scaffold for medicinal chemistry. The present work is focused on the use of α-cyano-*o*-tolunitrile, also known as homophtalonitrile, in various multicomponent reactions. Firstly, we developed a diastereoselective organocatalytic approach towards 12-(*o*-cyanophenyl)chromenoisoquinolinamines **1** through pseudo-three-component reaction of homophtalonitrile with o-hydroxybenzaldehydes.



1 70-92%
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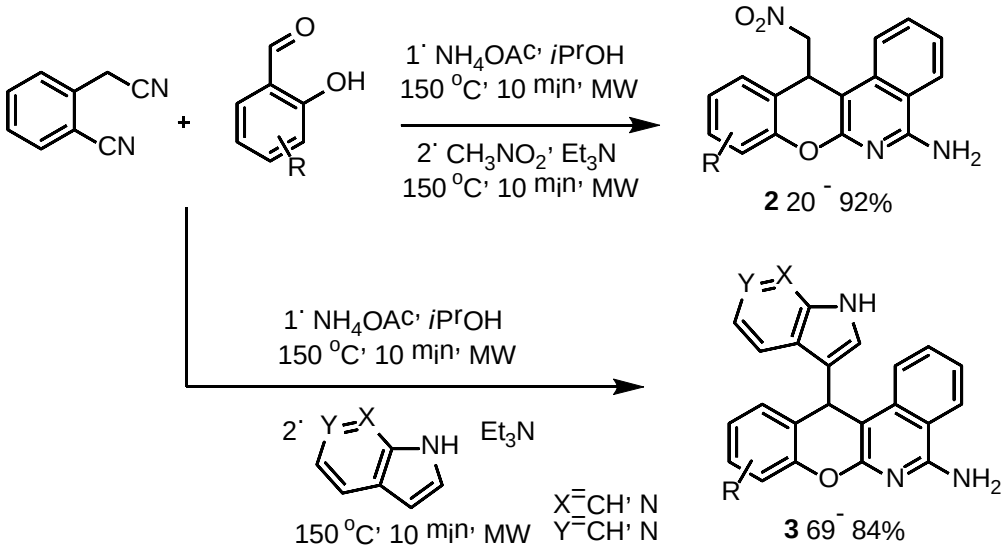
Secondly, a sequential three-component reaction of homophtalonitrile, o-hydroxybenzaldehydes, and nitromethane leading to formation of nitromethyl-substituted chromenoisoqunolines **2** has been studied. Thirdly, the exploitation of an indole as a nucleophile succeeded in formation of compounds **3**.



2 20 - 92%

3 69 - 84%

The work was prepared with the support of the "RUDN University Program 5-100" and RFBR grant 18-33-00536.

Phenyl boronic acids into the MCR chemical space: A useful addition to the medicinal chemistry tool box

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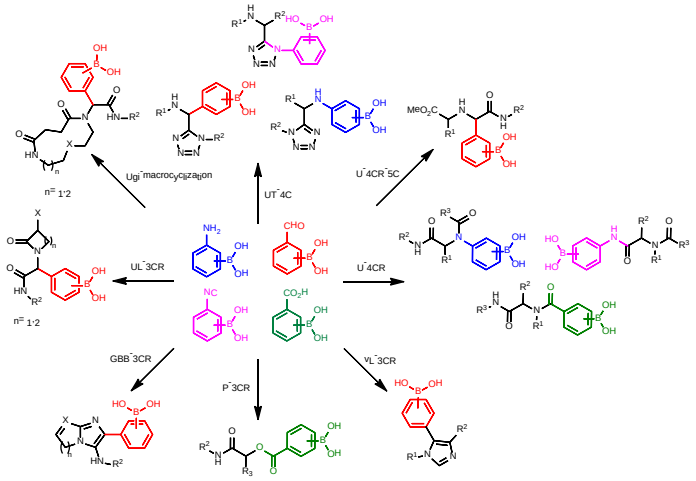
Boron is the nearest neighbor of carbon in the periodic table of elements and for this reason, the two elements share some similarities. However, boron differs from carbon due to its vacant p-orbital that is receptive to dative bond formation with oxygen nucleophiles. Specifically, boronic acids have the ability to act as “serine traps” under the influence of a serine hydrolase’s active site by forming metastable tetrahedral adducts with the catalytic serine; Boronic acid warheads are typically the most potent inhibitors of serine hydrolases. For all these reasons, boron-based compounds have a great potential in medicinal chemistry.

In continuation of our research on covalent inhibitors, we want to report our recent advances on incorporating different-substituted phenyl boronic acids into a diverse set of MCR scaffolds. A thorough analysis on the scope and limitations of the MCR reactions involving unprotected phenyl-boronic acids has been performed. We utilized substituted amino-, formylo- carboxy- and even isocyano-phenyl boronic acids in the most known MCRs such as U-4CR, U-4CR-5C, UT-4CR, vL-3CR, GBB-3CR and P-3CR. In addition, we were able to assemble phenyl boronic acids into drug-like scaffolds as β- or γ-lactams and macrocycles. Increasing even more the diversity and complexity of the synthesized derivatives, we performed in a one-pot process, Suzuki coupling reactions with different MCR scaffolds without the need of protecting groups.



[1] P. C. Trippier, C. McGuigan, *Medchemcomm* **2010**, *1*, 183.
[2] D. Gillingham, *Org. Biomol. Chem.* **2016**, *14*, 7606–7609.
[3] J. Tan, A. B. Cognetta III, D. B. Diaz, K. M. Lum, S. Adachi, S. Kundu, B. F. Cravatt, A. K. Yudin, *Nat. Commun.* **2017**, *8*, 1760.
[4] Z. J. Leśnikowski, *Expert Opin. Drug Discov.* **2016**, *11*, 569–578.
[5] M. Lanier, D. C. Cole, Y. Istratiy, M. G. Klein, P. A. Schwartz, R. Tjhen, A. Jennings, M. S. Hixon, *J. Med. Chem.* **2017**, *60*, 5209–5215.
[6] M. Groll, C. R. Berkers, H. L. Ploegh, H. Ovaa, *Structure* **2006**, *14*, 451–456.
[7] R. Smoum, A. Rubinstein, V. M. Dembitsky, M. Srebnik, *Chem. Rev.* **2012**, *112*, 4156–4220.
[8] A. Zajdlik, Z. Wang, J. L. Hickey, A. Aman, A. D. Schimmer, A. K. Yudin, *Angew. Chemie* **2013**, *125*, 8569–8573.

Multicomponent strategies for the construction of the analogues of spiro[pyrrolidine-3,3'-oxindole] alkaloids

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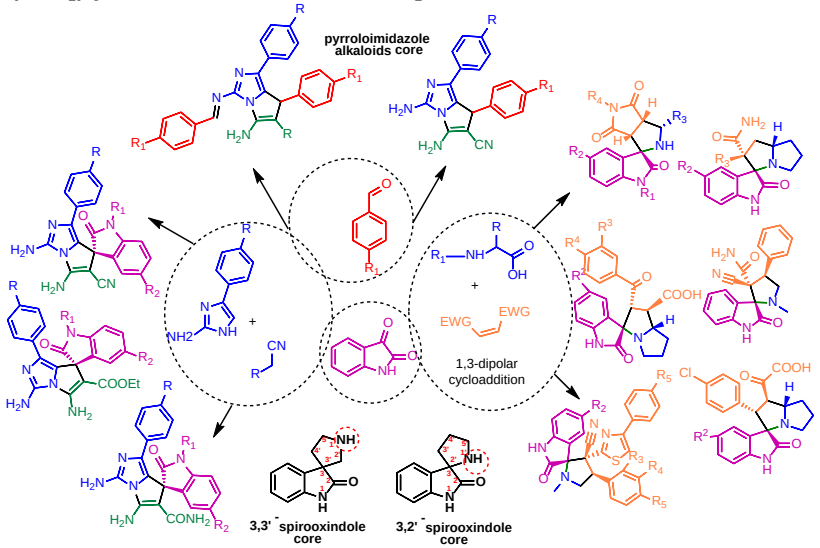
The spiro[pyrrolidine-3,3'-oxindole] moiety is present as a core in number of alkaloids with substantial biological activity. This fragment is prevalent in a number of spiro leader-compounds and drug candidates of different directions of action. The investigations of the efficient synthetic routs to compounds with spiroheterocycles or spirocarbocycles at C-2 or C-3 positions of indole system have increasingly appeared in the recent publications. Evidently among the different synthetic strategies, multicomponent reactions (MCRs) are dominating. The 1,3-dipolar cycloaddition reactions of azomethine ylides, generated in situ through the decarboxylative condensation of isatins and α-amino acids, with various dipolarophiles, are regarded as one of the most useful processes in the synthesis of the five membered heterocyclic ring. We have used this methodology for the regioselective construction of the spiro[pyrrolidine-3,2'-oxindole] systems based on maleimides, amides of acrylic acid, aroylacrylic acids, acrylonitriles and arylidenepyruvic acids.

From the other point of view, the presence of four nonequivalent nucleophilic centers in 2-amino-4-arylimidazoles creates unambiguity in the direction of their interaction with bielectrophiles. We have determined that condensation of aromatic aldehydes with 2-amino-4-arylimidazoles and acyclic CH-acids leads to the formation of novel 7H-pyrrolo[1,2-c]imidazole ring systems. Replacement of aldehydes by isatins give 3,3'-spirooxindole fused pyrrolo[1,2-c]imidazoles that can be considered as direct analogues of spiro[pyrrolidine-3,3'-oxindole] alkaloids.



References:

1 T. L. Pavlovskaya, R. Gr. Redkin, D. V. Atamanuk, V. V. Lipson, *Mol. Diversity* **2016**, *20*, 299-344..

2 T. L. Pavlovska, V.V. Lipson, S. V. Shishkina, V. I. Musatov, J. A. Nichaenko, V. V. Dotsenko, *Chem. Het. Compounds.* **2017**, *53*, 460-467.

Controlled Doebner-, Groebke- and Ugi-type Multicomponent Reactions Involving Aminoazoles with Further *In Vitro* Antibacterial and Antiviral Activity Evaluation Studies of the Reaction Products

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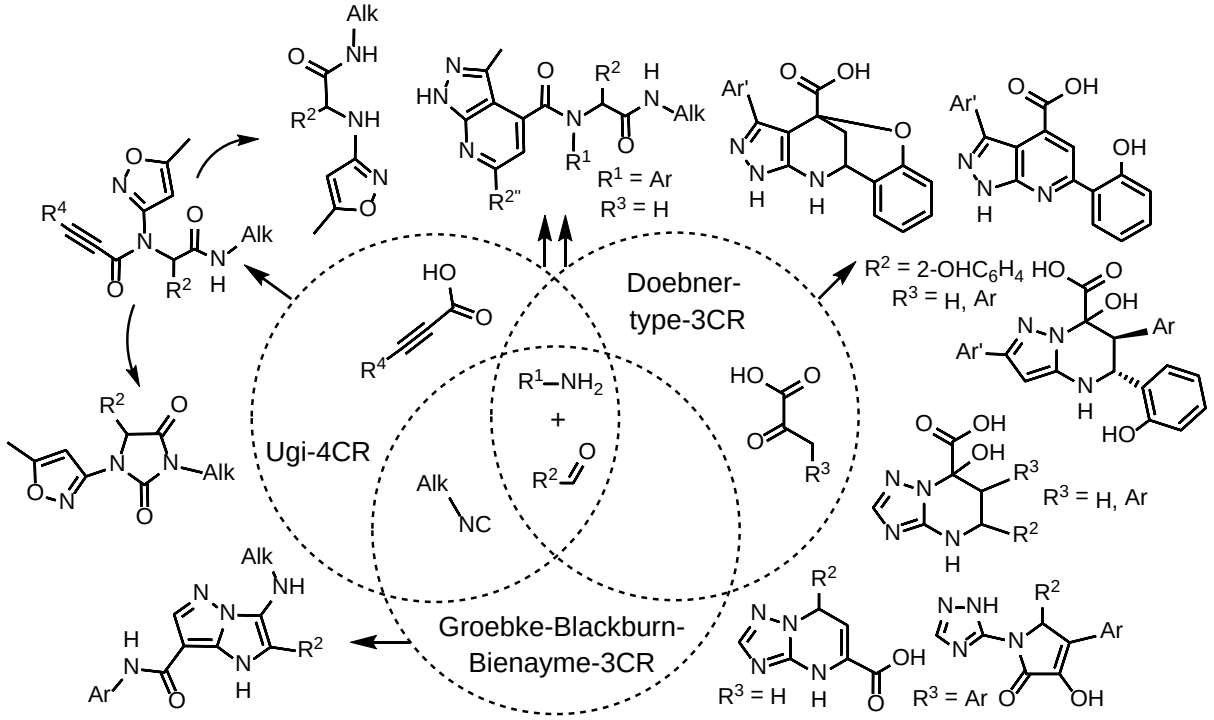
Recently the focus of Organic Chemistry has concentrated on the creation of libraries of structurally complex compounds for filling and systematical investigation of the chemical space within the concepts of Diversity and Medical oriented syntheses with the aim of finding new biologically active compounds.[1-3] From this point of view, MCRs, i.e. of Doebner-[2] and Ugi-types,[3] and their combinations are the powerful tool to access the diversity as well as the complexity of final compounds in one-pot procedure.

In the present study the series of aminoazoles was applied in a controlled Doebner-3CR, Groebke-3CR and Ugi-4CR that were often followed by the subsequent post-transformations. Moreover, a modification of the classical Ugi-4CR by introducing pyrazolopyridine carboxylic acids previously synthesized in the Doebner-3CR[2] was carried out. Antimicrobial and antiviral activity of the compounds synthesized was studied as well showing their probiotic properties and activity against A/H1N1 virus.



References:

1 V. Chebanov, K. Gura, S. Desenko, *Top. Heterocycl. Chem*. **2010**, *23*, 41–84.
2 V. A. Chebanov, Y. I. Sakhno, S. M. Desenko, V. N. Chernenko, V. I. Musatov, S. V. Shishkina, O. V. Shishkin, C. O. Kappe, *Tetrahedron* **2007**, *63*, 1229-1242.
3 A. Dömling, *Chem. Rev.* **2006**, *106*(1), 17–89.

Diversity Driven Decoration and Ligation of Fullerene by Ugi and Passerini Multicomponent Reactions

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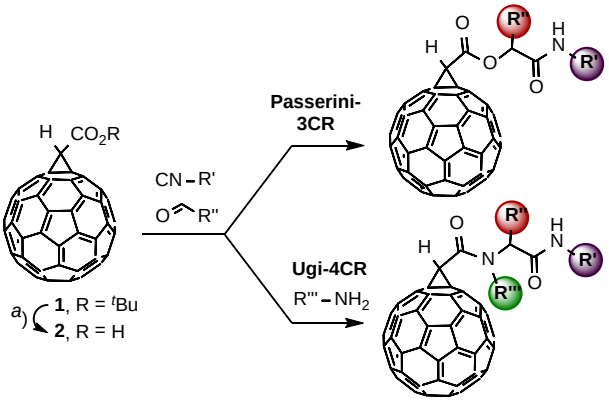
Aiming to provide an efficient and versatile method for the diversity-oriented decoration and ligation of fullerenes, we report the first C_{60} derivatization strategy based on isocyanide-multicomponent reactions (I-MCRs).[1] The approach comprises the use of Passerini and Ugi reactions for assembling pseudo-peptidic scaffolds on carboxylic acid-functionalized fullerenes. The method showed wide substrate scope for the oxo- and isocyanide components, albeit the Ugi reaction proved efficient only for aromatic amines. The approach was successfully employed for the ligation of oligopeptides and polyethyleneglycol chains (PEG) to C_{60}, as well as for the construction of bis-antennary as well as PEG-tethered dimeric fullerenes. In addition, post-Ugi modifications will be presented, leading to 7-component reactions.



[1] B. B. Ravanello, N. Seixas, O. E. D. Rodrigues, R. S. daSilva, M. A. Villetti, A. Frolov, D. G. Rivera,
B. Westermann, *Chem.-Eur. J.* **2018**, *DOI:* 10.1002/chem.201802414

Design of MCR scaffold with inhibitory activity on aspartic proteases

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Aspartic proteases represent a protein family with significant drug targets, including renin, HIV-protease, β-secretase (BACE-1) and plasmepsins. Various warheads have been studied for interacting either directly with the catalytic dyad of aspartic acids or indirectly mimicking the tetrahedral intermediate. Here we focus on endothiapepsin, a pepsin-like aspartic protease that has been studied excessively as a model enzyme both for elucidating the catalytic mechanism [1] and also in the clinical development of renin [2] and β-secretase inhibitors [3]. In this work, we designed a novel multi-component reaction (MCR) scaffold with the potential to interact with both acidic residues. The scaffold can be accessed via a two-step synthesis[4]. Preliminary screening results and crystallization studies supported the choice of the scaffold. Optimized derivatives were designed by docking virtual libraries and the selected hits were synthesized. Finally, novel crystal structures were obtained.

Acknowledgement: This project has received funding from the European Union's Framework Programme for Research and Innovation Horizon 2020 (2014 – 2020) under the Marie Skłodowska – Curie Grant Agreement No. 675555, Accelerated Early staGe Drug Discovery (AEGIS).

References:

1 L. Coates *et al. J. Am. Chem. Soc*. **2008**, *130(23*), 7235-37.
2 B. Veerapandian *et al*. *J. Mol. Biol*. **1990**, *216(4)*, 1017-29.
3 S. Geschwinder *et al*. *J. Med. Chem*. **2007**, *50(24*), 5903-11.
4 P. Patil *et al*. Synthesis **2016,** *48(08),* 1122-30**.**

Synthesis of highly functionalized 1,6-dihydropyridines via $Zn(OTf)_2$-catalyzed three-component cascade reaction of aldimines and two alkynes (IA^2-coupling)

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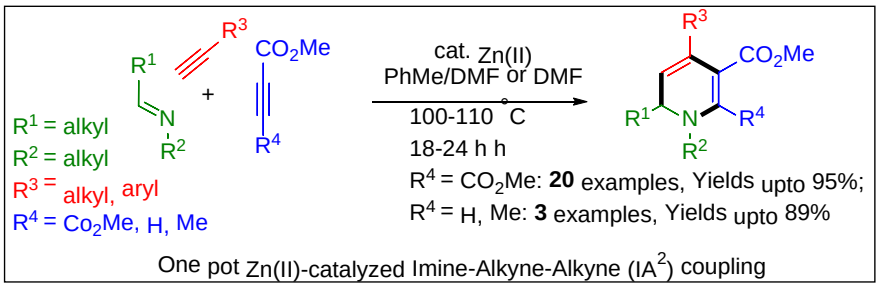

Although 1,4-dihydropyridines have attracted much more attention due to their wide biological and pharmaceutical applications, the biological applications of 1,2-/1,6-DHPs remained largely unexplored primarily because of the more challenging regioselectivity. For these reasons, the development of alternative methods for the selective synthesis of 1,2- or 1,6- dihydropyridines from readily available starting materials continues to be of intense interest.

Herein we describe a zinc(II) triflate catalyzed three component synthesis of 1,6-dihydropyridines, involving aldimines, alkynes and electron deficient dimethyl acetylenedicarboxylate (DMAD), in good to excellent yields. Besides a range of different N-substituents, a variety of both aromatic and aliphatic alkynes could be used. The application of electron deficient propiolates instead of DMAD, gave rise to regiospecific incorporation of the ester functionality on the 1,6- dihydropyridine ring. The reaction proceeds via a cascade involving nucleophilic addition of the metal acetylide to the imine, followed by addition of the intermediately formed propargylic amine to the electron deficient alkyne and subsequent 6-*endo dig* cyclization.

Trifluoroethanol Induces a Novel Five Component Reaction: Synthesis of 4-imidazolidinone Derivatives.

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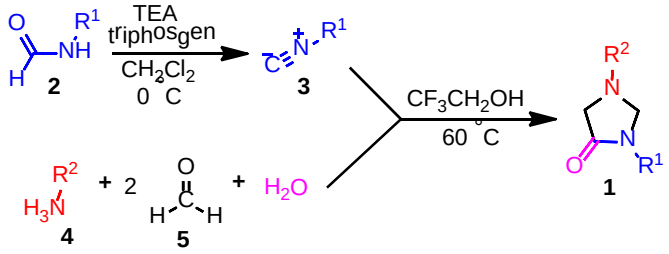
It is well known that a multi-component reaction (MCR) may be tuned by adapting the reaction conditions in order to generate different molecular scaffolds from the same starting materials.[1] For example, depending on the catalyst, solvent, or heating mode, the same component may react via different pathways to produce different scaffolds. While optimizing the conditions for the well-known Ugi-Smile reaction, we came across an unexpected result: when trifluoroethanol was used as solvent, a 4-imidazolidinone **1** was obtained instead of the desired product. In this context, we found a novel five component reaction which we have dubbed as the ARG-5CR, and which involves an isocyanide, a primary amine, two molecules of formaldehyde and water as an acid component.
In this work we describe the optimization of the reaction conditions and the scope of the procedure, which gave a good yield of the target compounds when a diverse set of alkylamines -both linear and branched- as well as functionalized amines and anilines were used. In the same way, a variety of isocyanides also reacted to render the corresponding imidazolidinones. Furthermore, as the procedure can be improved by generating the isocyanides *in situ*, thus avoiding the isolation of these ill-famed reactants[2,3], this new MCR becomes a valuable and faster alternative for the synthesis of this family of heterocycles when compared to the methods reported[4–7].



References:

1 E. Ruijter, R. Scheffelaar, R. V. a Orru, *Angew. Chemie - Int. Ed.* **2011**, *50*, 6234–6246.
2 C. G. Neochoritis, S. Stotani, B. Mishra, A. Dömling, *Org. Lett.* **2015**, *17*, 2002–2005.
3 A. Boltjes, *Org. Synth.* **2017**, *94*, 54–65.
4 C. E. Augelli-Szafran, B. D. Roth, A. Essenburg, K. L. Hamelehle, B. R. Krause, R. L. Stanfield, *Bioorganic Med. Chem. Lett.* **1994**, *4*, 1095–1100.
5 J. Liu, G. Cui, M. Zhao, C. Cui, J. Ju, S. Peng, *Bioorganic Med. Chem.* **2007**, *15*, 7773–7788.
6 J. Liu, M. Zhao, K. Qian, X. Zhang, K. H. Lee, J. Wu, Y. N. Liu, S. Peng, *Bioorganic Med. Chem.* **2010**, *18*, 1910–1917.
7 N. Vale, J. Matos, J. Gut, F. Nogueira, V. do Rosário, P. J. Rosenthal, R. Moreira, P. Gomes, *Bioorganic Med. Chem. Lett.* **2008**, *18*, 4150–4153.

Doing the trick: Combining Isocyanides with Carbon dioxide or Thiosulfonates

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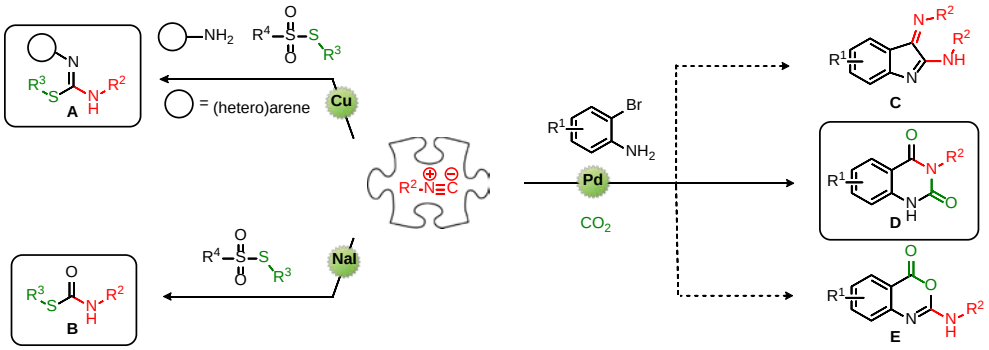
Isocyanides (R^2NC) are readily available and valuable C_1-reactants for organic synthesis.[1] They are especially valuable for multicomponent reactions as they allow library synthesis in a rapid and step-efficient manner. Our laboratories explored the combination of R^2NC with thiosulfonates ($R^4SO_2SR^3$) which gave access to novel methods towards isothiourea (**A**)[2] and thiocarbamates (**B**).[3] The *one-pot* nature of these reactions avoids multiple workups which is important in the context of *green* chemistry.[4] We recently also developed a Pd-catalyzed three-component synthesis of 2-bromoanilines, CO_2 and RNC. The combination of RNC and CO_2 is an attractive way to efficiently synthesize heterocycles, as in such an approach a carbonyl and imine moiety can be introduced simultaneously in the product. However, the combination of both in transition metal-catalyzed reactions is a challenge due to the difference in kinetic and thermodynamic stability of both C_1-reactants. While three different heterocycles (**C**, **D**, **E**) are potentially formed, our three-component reaction delivered *N*3-substituted quinazoline-2,4(1*H*,3*H*)-diones (**D**) in a completely regio- and chemoselective manner. The synthetic potential of our methodologies was illustrated by the formal synthesis of different APIs.



1. T. Vlaar, B. U. W. Maes, E. Ruijter, R. V. A Orru, *Angew. Chem. Int. Ed.* **2013**, *52*, 7084.
2. P. Mampuys, Y. Zhu, T. Vlaar, E. Ruijter, R. V. A Orru, B. U. W. Maes, *Angew. Chem. Int. Ed.* **2014**, *53*, 13063.
3. P. Mampuys; Y. Zhu, S. Sergeyev, E. Ruijter, R. V. A. Orru, S. Van Doorslaer, B. U. W. Maes, *Org. Lett.* **2016**, *18*, 2808.
4. S. Abou-Shehada, P. Mampuys, B. U. W. Maes, J. H. Clark, L. Summerton, *Green Chem.* ***2017***, *19*, 249.
5 P. Mampuys; H. Neumann, S. Sergeyev, R. V. A. Orru, H. Jiao, A. Spannenberg, B. U. W. Maes, M. Beller, *ACS Catal.* **2017**, *7*, 5549.

Rapid One-Pot Synthesis of Heterocycles by Sequentially Palladium-Catalysed One-Pot Processes

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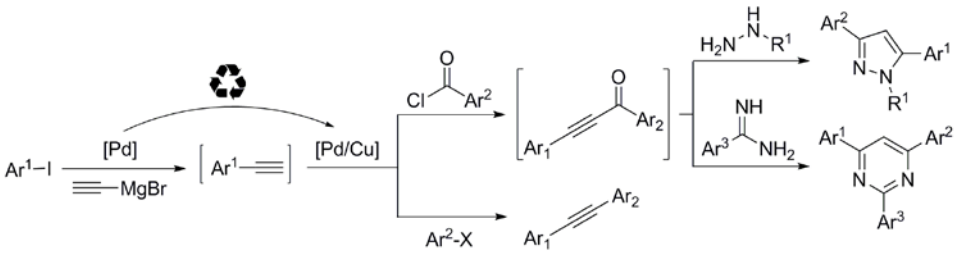
Unsymmetric alkynes are valuable building blocks in heterocycle synthesis that can also exhibit interesting properties for applications in molecular electronics. The most common approach to this class of molecules requires three steps, proceeding via the Sonogashira reaction of an aryl halide with trimethylsilyl acetylene, followed by deprotection and coupling with a second aryl halide or aroyl chloride.[1]

We herein present a protecting-group free, sequentially palladium-catalysed three component approach towards diarylalkynes and alkynones.[2] The intermediate terminal alkynes are generated in situ by a palladium-catalysed coupling of aryl iodides with ethynyl magnesium bromide,[3] followed by a Sonogashira coupling with no further addition of palladium catalyst necessary. The modular nature of the reaction, readily available starting materials, mild reaction conditions and short reaction time make it possible to synthesise a large variety of target molecules quickly and conveniently.



The sequence can be extended by a cyclocondensation of the resulting alkynones with dinucleophiles. A regioselective three step, four component one-pot synthesis of pyrazole[4] and pyrimidine[5] derivatives was successfully established using hydrazine derivatives and benzamidinium salts, respectively.[6]

We then examined the photophysical properties of selected donor-acceptor substituted pyrazoles. These compounds exhibit extraordinary Stokes shifts in solution and strong fluorescence solvatochromy. The experimental results were corroborated by DFT calculations.

In summary, we have developed a convenient and versatile sequentially palladium-catalysed strategy for the synthesis of unsymmetric alkynes and heterocycles. The reaction proceeds with a large variety of substrates and can be modified and extended to give access to different target molecules. No protecting groups are necessary and all reactants and catalysts are readily available and easy to handle.

References:

1 R. Chinchilla, C. Nájera, *Chem. Rev.* **2007**, *107*, 874–922.
2 A. C. Götzinger, T. J. J. Müller, *Org. Biomol. Chem.* **2016***,14,* 3498–3500.
3 E.-i. Negishi, M. Kotora, C. Xu, *J. Org. Chem.* **1997**, *62*, 8957–8960.
4 B. Willy, T. J. J. Müller, *Eur. J. Org. Chem.* **2008**, *24*, 4157–4168.
5 C. Boersch, E. Merkul, T. J. J. Müller, *Angew. Chem. Int. Ed.* **2011**, *50*, 10448–10452.
6 A. C. Götzinger, F. A. Theßeling, C. Hoppe, T. J. J. Müller, *J. Org. Chem.* **2016**, *81*, 10328–10338.

Highly convergent synthesis of fluorescent furo[2,3-*c*]isoquinolines coupling the Ugi reaction with a palladium-catalyzed cyclization cascade

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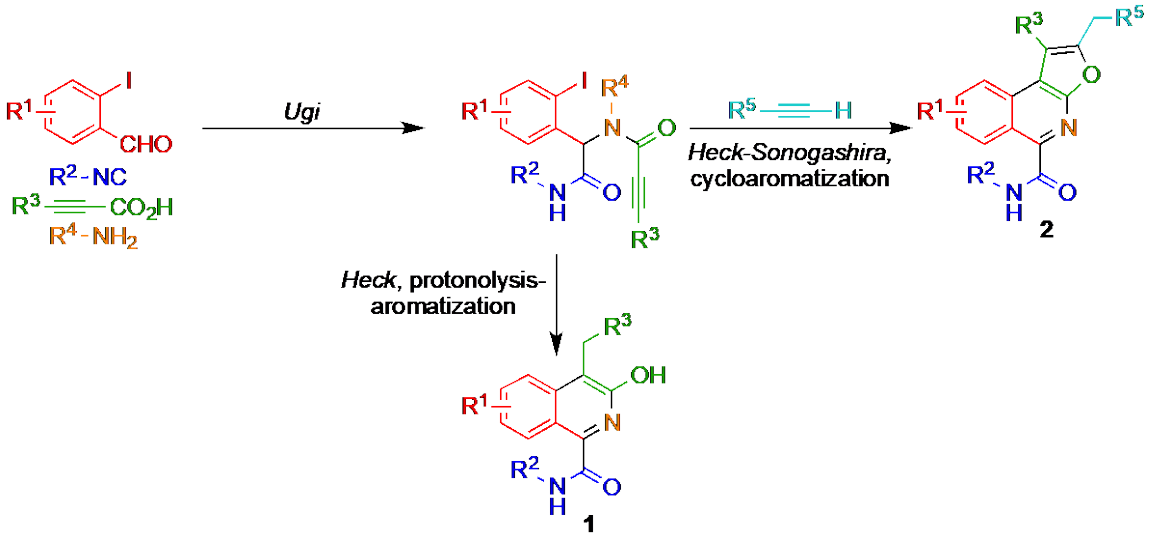
We recently developed an efficient method for the synthesis of highly substituted isoquinolines – namely 3-hydroxyisoquinolines **1** and furo[2,3-*c*]isoquinolines **2** – by coupling the Ugi reaction with:

a) a Heck cyclization, followed by a protonolysis-aromatization sequence;[1]
b) a complex palladium catalyzed cascade sequence, involving a Heck-Sonogashira reaction, followed by a cycloaromatization.[2]

The new heterocyclic molecules are all intensively blue emissive, in most cases with remarkable Stokes shifts and relative fluorescence quantum yields.
In order to have a deeper insight into the photophysical properties of the rather unknown and poorly investigated furo[2,3-*c*]isoquinoline scaffold, we decided to better understand the influence of the substituents and of an extended conjugation as well on the emission upon excitation by UV light.
Thanks to the possibility to fine tune the structure of all the substituents of the reagents involved in this complex sequence, we synthesized a second generation library of compounds **2** and studied their emission properties, including the aggregation induced emission (AIE).
The most recent results within this field will be presented.



References:

1 L. Moni, M. Denißen, G. Valentini, G., T. J. J. Müller, R. Riva, *Chem. Eur. J.* **2015**, *21*, 753.
2. L. Moni, C. Gers-Panther, M. Anselmo, T. J. J. Müller, R. Riva, *Chem. Eur. J.* **2016**, *22*, 2020.

Radical Simplification of Chemical Synthesis by MCRs Strategies.

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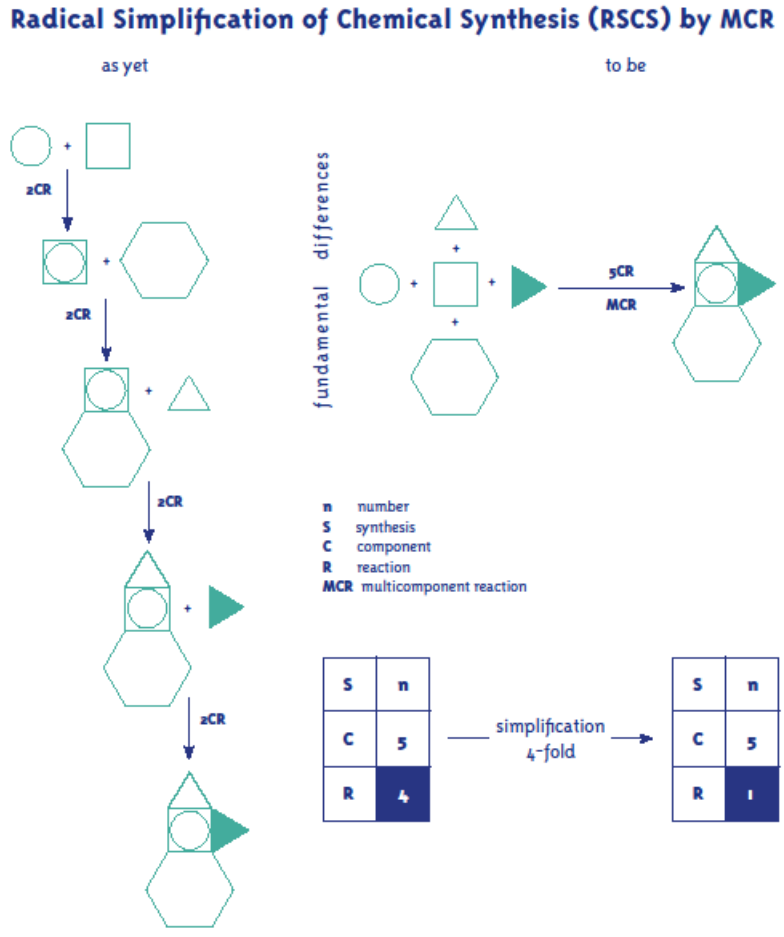
Important and expensive medicines for half, quarter or even tenth price, is that possible? Yes, that is possible through consistent application of the »radical and concerted simplification of chemical synthesis«.[1] This concept saves the most extensive resources and energy. Radical changes to essential industries are breaking ground at the start of this third millennium, but chemistry has not yet begun these, although the prerequisites for such a metamorphosis are already present in the form of MCRs.[2] These reactions open up the gate to an industrial innovation, creating a new path for manifold, inexpensive materials and substances which will benefit the whole world.



References:

1 H. Eckert, „Radical and Concerted Simplification of Chemical Synthesis I", *Wolff-Verlag, Berlin,* **2017**, ISBN: 978-3-941461-90-1.
2 H. Eckert, *Molecules* **2017**, *22*, 349(1-32).

Novel synthesis of (hetero)biaryls: when multicomponent reactions meet hyperbaric activation

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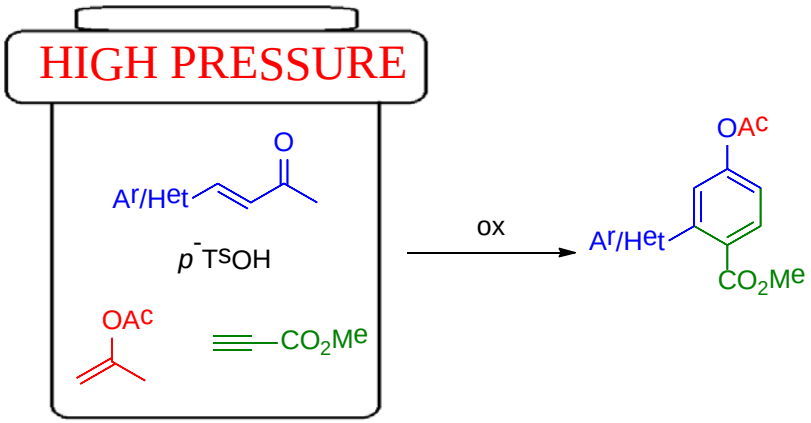
The unquestionable advantages of multicomponent reactions promoted their application in the synthesis of fascinating compounds, as noteworthy molecular complexity and variety cannot be as easily achieved through other synthetic approaches.[1]

In continuation of our studies on metal-free hyperbaric activation of alkynes in Diels-Alder reactions,[2] we envisaged the possibility of developing a multicomponent protocol to generate *in situ* a suitable diene *via* acid-catalyzed enolacetylation of the corresponding (hetero)arylideneacetone with isopropenyl acetate. This intermediate then undergoes high-pressure promoted Diels-Alder reaction in the presence of an electron-poor dienophile (*i. e.* methyl propiolate) to give the resultant cycloadduct. Interestingly, the reaction is completely regioselective and the cycloadducts can be easily oxidized to the corresponding (hetero)biaryls.[3]

This synthetic protocol is particularly interesting considering the ubiquity of (hetero)biaryls as key structural motif in a wide range of natural compounds, drugs, chiral auxiliaries, and high-performance molecules, like organic semiconductors and liquid crystals. Frequently, modern applications are not compatible with the presence of metal traces and therefore a metal-free multicomponent annulation strategy is even more attractive from an economic point of view, avoiding the purchase or synthesis of expensive metal catalysts and ligands as well as time and money consuming final purifications.



References:

1. A. Galván, F. J. Fañanás, F. Rodríguez *Eur. J. Inorg. Chem.* **2016**, 1306.
2. L. Minuti, A. Temperini, E. Ballerini *J. Org. Chem.* **2012**, 77, 7923.
3. L. Minuti, F. Piazzolla, A. Temperini *Eur. J. Org. Chem.* **2017**, 36, 5370.

Isocyanide Based Multicomponent Reaction of Diamines: Further Expansions, Modifications, and Applications for Focused Libraries Design and Synthesis

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Isocyanide-based multicomponent reactions (IMCR) have become a valuable resource-economy synthetic tool of medicinal chemistry since they make easily accessible drug- and nature-like small molecules with privileged heterocyclic cores. Recently, we have developed a novel IMCR that leads to 2-amino-1,4-diazaheterocycles starting from diamines and carbonyl compounds in one simple synthetic step. The IMCR has been shown to be applicable for a wide range of diamines, carbonyl compounds, and isocyanides, whose structural variety defines diversity of obtainable amino-azaheterocycles.

Herein we report further expansions of the discovered IMCR including synthesis of unique spiro-fused heterocyclic scaffolds, post-IMCR modifications that lead to pharmacologically relevant heterocycles with annulated imidazole moiety. The IMCR and its modifications have been successfully applied for design and synthesis of focused libraries such as potential toll-like receptor TLR-7, beta-secretase (BASE), nitric oxide synthetase (NOS-2) ligands, orexin receptor and cannabinoid receptor CB2 antagonists, mGlur5, TGR5 and RAR-related orphan receptor gamma (RORγ) modulators, and others.

Multicomponent Synthesis of 4-Aminoquinolines via an Imidoylative Sonogashira coupling/Cycloaromatization Sequence

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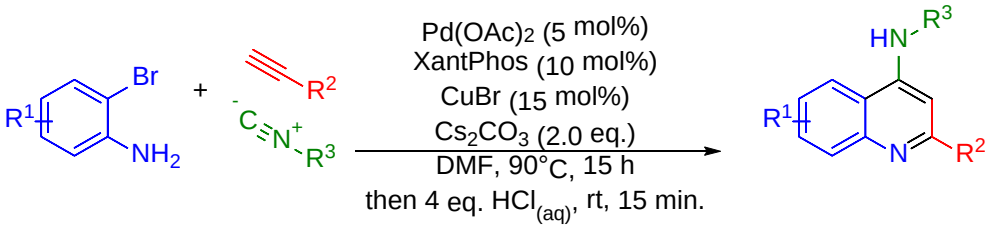
Abstract

In light of our continued interest in the use of palladium-catalyzed isocyanide insertion[1] for the synthesis of drug-like heterocycles, we developed an efficient route to substituted 4-aminoquinolines. Medicinally valuable 4-aminoquinolines were synthesized in a one-pot procedure from commercially available *o*-bromoanilines, alkynes and isocyanides. The reaction proceeds via an efficient imidoylative (isocyanide insertive) Sonogashira coupling/ cycloaromatization sequence.[2] Although electron-deficient substrates led to somewhat diminished yields, the reaction is highly tolerant of secondary and even primary isocyanides. Additionally, this three-component annulation can be employed to smoothly afford substituted analogs of the known antimalarial drug chloroquine in high yield, in a one-pot manner. In this presentation the scope, limitations and some mechanistic aspects of this novel Pd-catalyzed three component coupling will be discussed in detail.



[1] For a review, see: Vlaar, T.; Ruijter, E.; Maes, B.U.W.; Orru, R.V.A. *Angew. Chem. Int. Ed.* **2013**, *52*, 7084-7097.
[2] Collet, J.W.; Ackermans, K.; Lambregts, J.; Maes, B.U.W.; Orru, R.V.A.; Ruijter, E. *J. Org. Chem.* **2018**, *83*, 854-861.

Simple Organocatalysts in Multi-Step Reactions: An efficient one-pot Morita-Baylis-Hillman-Type α-Hydroxylation of Vinyl Ketones followed by the convenient, temperature-controlled One-Pot-Etherification using Alcohols

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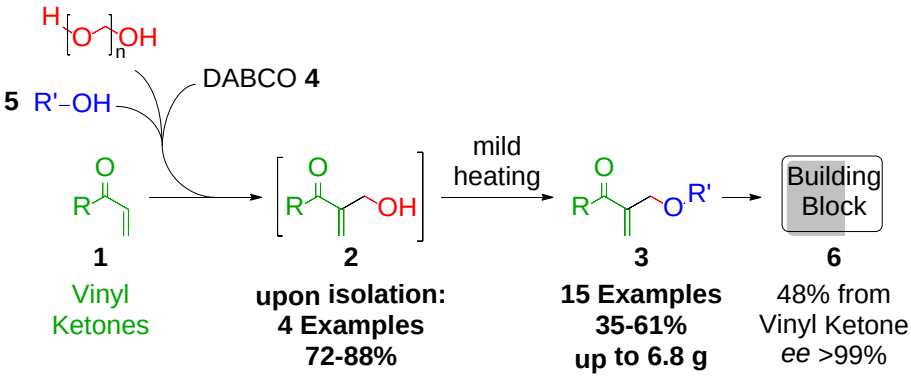
Powerful in combining simplicity, economic advantages, and broad synthetic applicability, the Morita-Baylis-Hillman (MBH) reaction has become a valuable tool for the organic synthetic chemist being employed for asymmetric and non-stereoselective applications alike. Concerning the latter, the α-hydroxymethylation of Michael-systems using formaldehyde has to be named as a simple, yet important reaction with respect to the products' vital role in total synthesis and polymer science. Additionally, not only the MBH-products themselves, but also their OH-protected analogues have proven to be valuable compounds for various purposes.[1] Nevertheless, a high yielding procedure towards vinyl-ketone **1** based MBH-products **2** bearing electronically different residues is hardly available and a synthetically useful access to the OH-protected analogues **3** without pre-activation of either one of the coupling partners remains unknown.



We herein present an approach providing good to very good yields for the conversion of various vinyl ketones **1** with formaldehyde in MBH-type reactions with low loadings of the inexpensive ca-talyst 1,4-diazabicy-clo[2.2.2]octane (DABCO, **4**). Furthermore, for the first time OH-protected MBH-products **3** can be prepared in moderate to good yields and high purities over two steps on a multi-gram scale without any pre-activation of the alcohols being coupled and a in total three time utilization of the same organo-catalyst during the course of the reaction. In addition to the multiple use of the amine-catalyst, a threefold employment of alcohol **5** during the described procedure enables an altogether atom-efficient access to a broad scope of MBH-product based ethers **3**. Finally, the use of the products obtained is demonstrated by a highly stereoselective, gram-scale preparation of building blocks **6** prominent in total synthesis.[2]

References:

1 D. Basavaiha, G. Veeraraghavaiah, *Chem. Soc. Rev.* **2012**, *41*, 68-78; S. Bhowmik, S. Batra, *Curr. Org. Chem.* **2014**, *18*, 3078-3119; C. Peng, A. Joy, *Macromolecules* **2014**, *47*, 1258-1268.
2 M. Mantel, M. Guder, J. Pietruszka, *accepted.*

Merging Heterocyclic Chemistry and Biocatalysis: Enantioselective Reduction of Sulfur-containing Cyclic Imines Prepared *via* Asinger-type Multicomponent Reaction

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National Academy of Science of Ukraine, UkraineSulfur-containing cyclic amines play an important role in nature and medicine. In particular this is true for the 3-thiazolidine ring, which represents a structural motif in penicillins, derived β-lactam antibiotics, HIV protease inhibitors and an industrial intermediate for the production of D-penicillamine. Conceptually a general access to 3-thiazolidines (**2**) could proceed through reduction of the C=N double bond in 3-thiazolines (**1**), which can be elegantly prepared *via* Asinger-type multicomponent reaction.[1] However, in spite of the availability of such attractive substrates, in all research work going back to the 1950ies up to now reduction of 3-thiazolines (**1**) failed by means of nearly all “state of the art”-type chemical reduction technologies for imines.[2] Thus, the development of an efficient general method for the reduction of 3-thiazolines (**1**) represented a remaining challenge as well as establishing a highly asymmetric version of this reaction. Attracted by the recent successful use of imine reductases for various reductions of cyclic imines,[3] we became interested to study the suitability of such enzymes for the reduction of 3-thiazolines as well as 2*H*-1,4-benzothiazines to the corresponding cyclic amines.

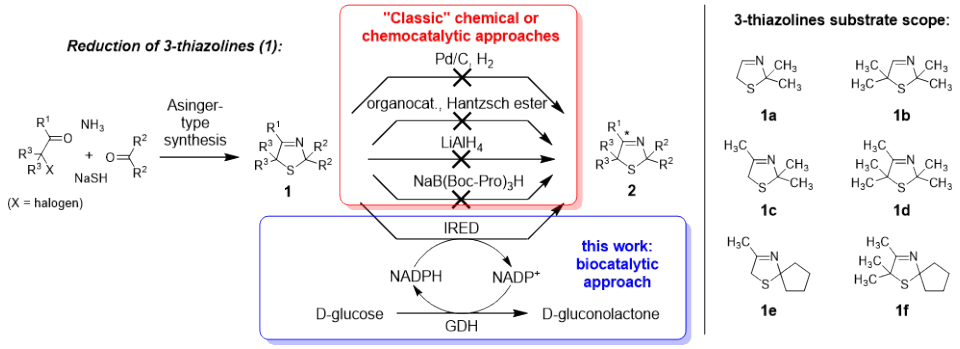

Figure 1. Concept and examined substrate scope of 3-thiazoline reduction.

We present the first method enabling a reduction of 3-thiazolines under formation of 3-thiazolidines with high conversion and high to excellent enantioselectivity (>96% *ee* and 99% *ee* in most cases), avoiding undesired ring-opening or other side reactions. This process technology has a broad substrate range and could also be applied successfully to other sulfur-containing heterocyclic imines such as *2H*-1,4-benzothiazines. Furthermore, a process development was conducted and a cascade reaction towards a one-pot synthesis of 3-thiazolidines was established.

1 a) Review: F. Asinger, H. Offermanns, Angew. Chem. 1967, 79, 953-1028; Angew. Chem. Int. Ed. Engl. 1967, 6, 907-919; b) F. Asinger, Angew. Chem. 1956, 68, 413; c) F. Asinger, M. Thiel, Angew. Chem. 1958, 70, 667-683; K. Drauz, H. G. Koban, J. Martens, W. Schwarze, Liebigs Ann. Chem. 1985, 1985, 448-452.
2 a) M. Thiel, F. Asinger, K. Häussler, T. Kröner, Liebigs Ann. 1959, 622, 107-117; b) N. Zumbrägel, H. Gröger, unpublished results; c) I. Reiners, H. Gröger, J. Martens, J. Prakt. Chem. 1997, 339, 541-546.
3 a) D. Wetzl, M. Berrera, N. Sandon, D. Fishlock, M. Ebeling, M. Müller, S. Hanlon, B. Wirz, H. Iding, ChemBioChem 2015, 16, 1749-1756; b) Review: G. Grogan, N. J. Turner, Chem. Eur. J. 2016, 22, 1900-1907.

Use of biocatalytic chiral bio-based starting material in the Hosomi-Sakurai multicomponent reaction

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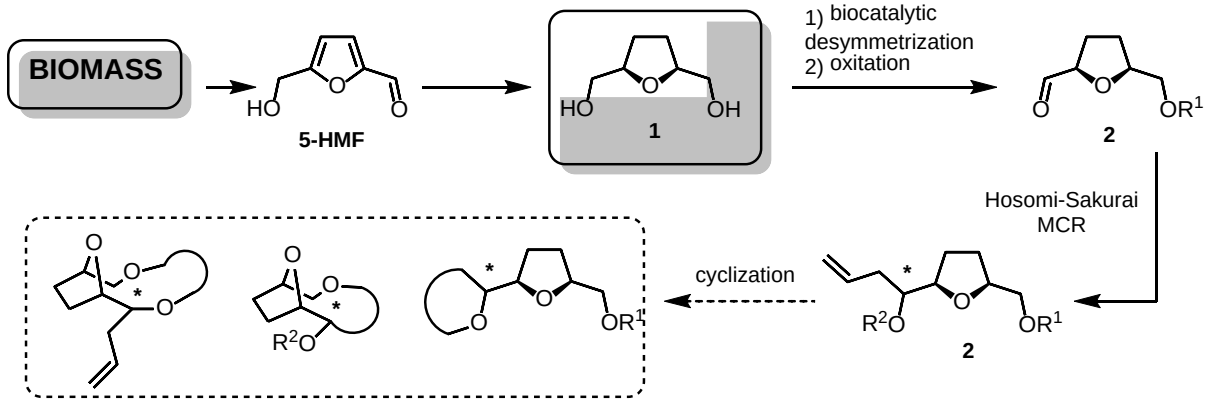
Multicomponent reactions (MCR) are a powerful strategy for the preparation of complex organic molecules from easily available starting materials with high atom and step economy. Among the others, the three-component Hosomi-Sakurai (H-S) MCR is quite unexplored, in particular when chiral aldehydes are employed.[1,2]
The use of building blocks obtained from biomass[3] in such reactions is particularly interesting in the context of bioeconomy and allow the preparation of bio-based fine chemicals with high added value. So far, the exploitation of such bio-based starting materials has been mainly focused to the production of low cost commodities, such as biopolymers.
In this context, we have pointed our attention to the use of 5-hydroxymethylfurfural (5-HMF) and its derivatives. 5-HMF is a compound obtainable from dehydration process of natural polysaccharides of common hexoses and can be further converted to the *meso* diol **1** by hydrogenation. By a key enzymatic desymmetrization, we envisaged the possibility to obtain the chiral aldehyde **2** that can be subjected, together with a silyl ether and an allylsilane, to the H-S MCR allowing the preparation of chiral homoallylic ethers. Further evolution by a cyclization process can lead to unusual cyclic ethers.
Herein, we report the identification and the preparation of the suitable chiral 5-HMF-deriving building block for the Hosomi-Sakurai MCR and the study of its reactivity in the preparation of homoallylic ethers.



References:
1 A. Mekhalfia, I. E. Markò, *Tetrahedron Lett.* **1991**, *32*, 36, 4779–4782.
2 J. Pospisil, T. Kumamoto, I. E. Markò, *Angew. Chem. Int. Ed.* **2006**, *45*, 3357–3360.
3 F. H. Isikgor, C. R. Becer, *Polym. Chem.* **2015**, *6*, 4497–4559.

Access to heterocycles from organosilanes

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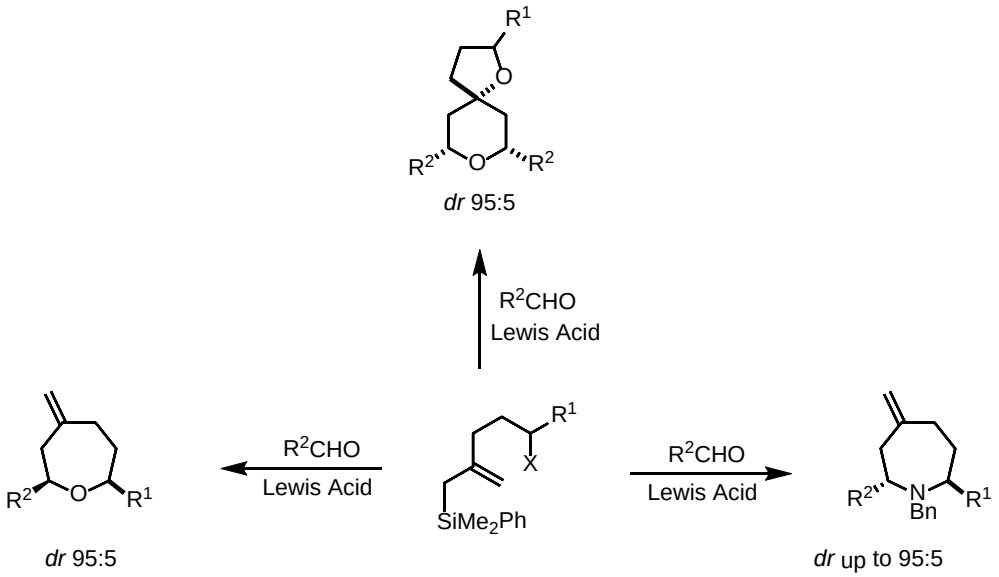
Oxygen and nitrogen heterocycles are structural motifs present in a large number of biologically active natural products.[1] Within the strategies employed for the synthesis of these compounds, Prins cyclization has emerged as a very efficient protocol. The use of electron-rich alkenes, such as organosilanes, in this reaction (the so-called silyl-Prins cyclization) implies more selective processes.
Herein, we present our last results towards the synthesis of different sized oxa- and azacycles via silyl-Prins cyclizations of allylsilyl alcohols and amines.[2-5]



References:

1. T. Yasumoto, M. Murata, *Chem. Rev*. **1993**, *93*, 1897.
2. A. Barbero, A. Diez-Varga, F. J. Pulido, *Org. Lett*. **2013**, *15*, 5234.
3. A. Diez-Varga, H. Barbero, F. J. Pulido, A. González-Ortega, A. Barbero, *Chem. Eur. J.* **2014**, *20*, 14112.
4. A. Barbero, A. Diez-Varga, M. Herrero, F. J. Pulido, *J. Org. Chem*. **2016**, *81*, 2704.
5. A. Barbero, A. Diez-Varga, F. J. Pulido, A. González-Ortega, *Org. Lett*. **2016**, *18*, 1972.

Concise approach toward the synthesis of spirocyclic isoquinolinediones via Rh(II) catalyzed C-O insertion protocol

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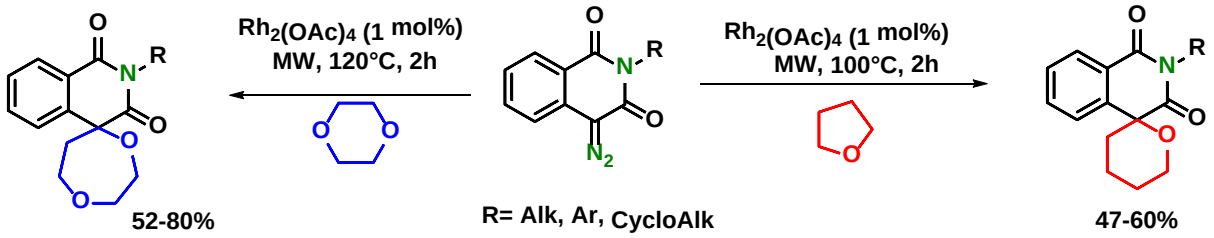
Spirocyclic compounds found widespread interest in medicinal chemistry and drug discovery[1]. Various bioactive compounds, both natural and synthetic, possess a spirocyclic ether core. The presence of spiro center enhances the rigid three-dimensionality of the molecule and promises higher binding affinity to a protein target. The biological and therapeutic value of spirocyclic scaffolds provokes the elaboration of novel methods for their synthesis. Recently,[2] a convergent approach towards diverse spirocyclic ethers via rhodium carbenoids was described. Taking into account the high reactivity of carbenoids and their ability to insert into C-O, C-S, and C-N bonds we were interested whether homophthalimidcarbenes can be substrates in these transformation.

Herein, we present a facile access to spirocyclic isoquinolinediones by Rh(II) catalyzed insertion of *in situ* generated homophthalimidcarbenoids in the C-O bonds of THF or 1,4-dioxane. The reaction proceeds smoothly under microwave irradiation in the presence of 1 mol% of $Rh_2(OAc)_4$ that was found best catalyst for this transformation, furnishing spirocyclic isoquinolinediones with moderate to good yields. It is noteworthy to mention that the formation of polyoxygenated[3] 8- and 9-membered fused systems was not observed.



References:

1 Y. Zheng, C. M. Tice, S. B. Singh, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3673-3682.
2 A. C. Hunter, S. C. Schlitzer, J. C. Stevens, B. Almutwalli, I. Sharma, *J. Org. Chem*. **2018**, *83*, 2744−2752.
3 R. Ballestros-Garrido, D. Rix, C. Besnard, J. Lacour, *Chem. Eur. J.* **2012**, *18*, 6626−6631.

A Gold-Catalyzed Domino Cyclization Enabling Rapid Construction of Diverse Polyheterocyclic Frameworks

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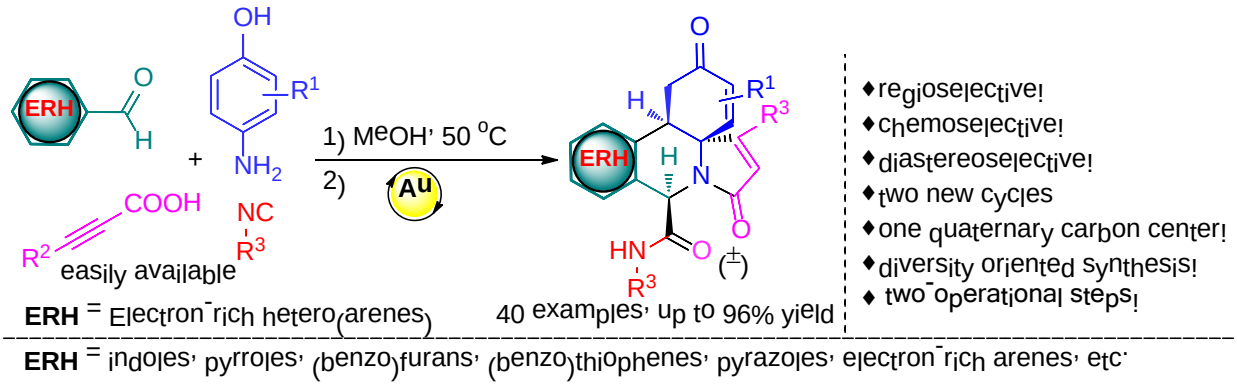
Abstract: We report herein an efficient gold(I)-catalyzed post-Ugi domino dearomatization/ipso-cyclization/Michael sequence that enables access to libraries of diverse (hetero)arene-annulated tricyclic heterocycles. This process affords novel complex polycyclic scaffolds in moderate to good yields from readily available acyclic precursors with excellent chemo-, regio-, and diastereo-selectivity. The power of this strategy has been demonstrated by the rapid synthesis of 40 highly functionalized polyheterocycles bearing indole, pyrrole, (benzo)furan, (benzo)thiophene, pyrazole and electron-rich arenes in two-operational steps.



New Multicomponent Reactions of Aminoazoles: Synthesis of Adenine Isosteres and Beyond

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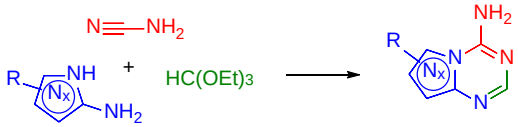
Multicomponent reactions have gain recognition in organic chemistry as an efficient synthetic methodology providing atom-economy, step-efficiency, and cost-effectiveness of the process. Aminoazoles were found to be useful synthons for the construction of diverse heterocyclic compounds in various multicomponent reactions.[1] Our group developed a new multicomponent reaction, which was demonstrated to be general and selective for many substituted aminoazoles. It is particularly useful for the annulation of the aminotriazine ring, thus resulting in the formation of several heterocyclic analogues of adenine. This type of compounds represents 1,3,5-triazine based isosteres of purines known to be a privileged scaffold in medicinal chemistry.[2]

The developed reaction involves interaction of aminoazoles with cyanamide and triethyl orthoformate as outlined in the general scheme below. The reaction required high temperature and thus was usually performed in microwave synthesizers. The results were reproducible in several commercial microwave reactors with minimal deviations in the outcome. Under optimized reaction conditions, the products were also obtained in satisfactory yields in the reactor operating under conventional heating, when the reaction parameters (temperature and pressure) were adjusted to those used in the microwave synthesizers.

The scope of the reaction was rather broad and it was effectively performed using as substrates: 5(3)-amino-1,2,4-triazoles, including 3,5-diamino- substituted analogues,[3,4] variously substituted 5(3)-aminopyrazoles,[5-8] 2-aminoimidazoles,[9] and other aminoazoles. Other trialkyl orthoformates, e.g. the trimethyl ester, were also effectively used this reaction. Moreover, the reaction conditions could be optimized for the efficient use orthoestes of other carboxylic acids. Additionally, new interesting rearrangements were observed for several aminoazoles used as substrates for the multicomponent reaction with cyanamide and trialkyl orthoesters.

Some structural features of the prepared adenine analogues were explored in details using dynamic NMR spectroscopy and X-ray crystallography. The pharmacological properties of the prepared compounds are also under investigations.



1 V. A. Chebanov, K. A. Gura, S. M. Desenko, *Top. Heterocycl. Chem*. **2010**, *23*, 41-84.
2. F. P. L. Lim, A. V. Dolzhenko, *Eur. J. Med. Chem*. **2014**, *85*, 371-390.
3. S. A. Kalinina, D. V. Kalinin, A. V. Dolzhenko, *Tetrahedron Lett.* **2013**, *54*, 5537-5540.
4. A. V. Dolzhenko, S. A. Kalinina, D. V. Kalinin, *RSC Adv*. **2013**, *3*, 15850-15855.
5. F. P. L. Lim, G. Luna, A. V. Dolzhenko, *Tetrahedron Lett*. **2014**, *55*, 5159-5163.
6. F. P. L. Lim, G. Luna, A. V. Dolzhenko, *Tetrahedron Lett*. **2015**, *56*, 7016-7019.
7. F. P. L. Lim, G. Luna, A. V. Dolzhenko, *Tetrahedron Lett*. **2015**, *56*, 521-524.
8. F. P. L. Lim, N. R.Halcovitch, E. R. T. Tiekink, A. V. Dolzhenko, *Tetrahedron* **2018**, *74*, 1868-1879.
9. F. P. L. Lim, S. T. Low, E. L. K. Ho, N. R. Halcovitch, E. R. T. Tiekink, A. V. Dolzhenko, *RSC Adv*. **2017**, *7*, 51062-51068.

Replacing Homogenous Noble Metal Catalysts with Base-Metal Alternatives: from Concepts to Sustainable Multicomponent Transformations

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Over the last decades, transition metal catalysis has been further developed and plays a crucial role in the chemical and pharmaceutical industries. In recent years, efforts have been made to develop processes that can be catalyzed by more earth-abundant metals.[1]

In this talk, I will present an overview on our research in this area. That will include the discovery of the first iron catalyzed dehydrogenation–hydrogenation of alcohols as well as hydrogenation–racemization of the pro-chiral ketones in combination with a lipase catalyzed kinetic resolution. Our novel iron/lipase catalytic system has proved broad applicability in the one pot dynamic kinetic resolution of alcohols as well as the cascade reductive acylation of ketones (Figure 1a).[2,3] Furthermore, during our investigations on the use of iron tricarbonyl complexes as hydrogenase mimics we observed an unexpected hydrofunctionalization of allenic alcohols and amines which give access to valuable oxygen and nitrogen heterocycles. Combined experimental and computational studies have explained the new concept. The iron complex exhibits a dual catalytic role in substrate activation, when the non-innocent cyclopentadienone ligand acts as proton shuttle in the isomerization and demetalation steps (Figure 1b).[4,5]

Noteworthy, the presentation will highlight our most recent research on the use of novel air stable manganese pincer complexes in different unprecedented environmentally benign (de)hydrogenation reactions[6] as well as new concepts in the multicomponent synthesis of heterocycles.[7]

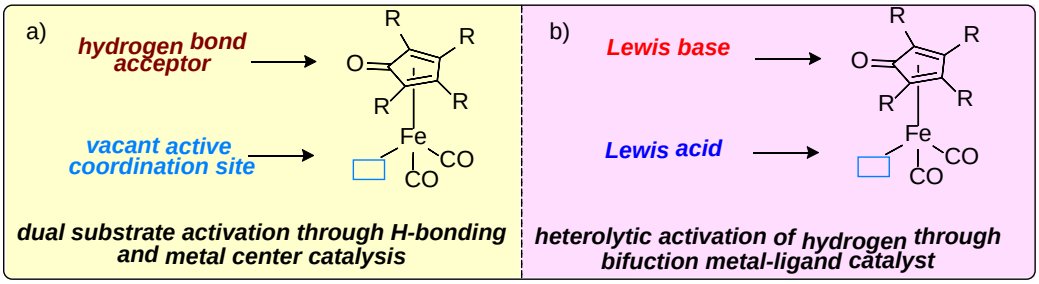

Figure 1. The catalytic concepts of the iron tricarbonyl complexes

1. Bullock, R. M. *Catalysis without Precious Metals*, **2010**, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany
2. El-Sepelgy, O. ; Alandini, N. ; Rueping, M. *Angew. Chem Int. Ed*. **2016**, *55*, 13602.
3. El-Sepelgy, O. ; Brzozowska, A. ; Rueping M. *ChemSusChem* **2017**, *10*, 1664.
4. El-Sepelgy, O. ; Brzozowska, A. ; Azofra, L. M. ; Jang, Y. K. ; Cavallo, L. ; Rueping, M. *Angew. Chem. Int. Ed.* **2017**, *56*, 14863.
5. El-Sepelgy, O. ; Brzozowska, A. ; Sklyaruk, J. ; Jang, Y. K. ; Zubar, V. ; Rueping, M. Org. *Lett.* **2018**, *20*, 696.
6. For a representative example see: Brzozowska, A.; Azofra, L. M.; Zubar, V.; Atodiresei, I.; Cavallo, L.; Rueping, M.; El-Sepelgy, O. *ACS Catal.* **2018**, *8,* 4103.
7. *In the Publication Process*

Canceled

Synthesis of Cyclic Hydroxamic Acids by the Formal [2+4] Cycloaddition of Oximes and Homophthalic Anhydride

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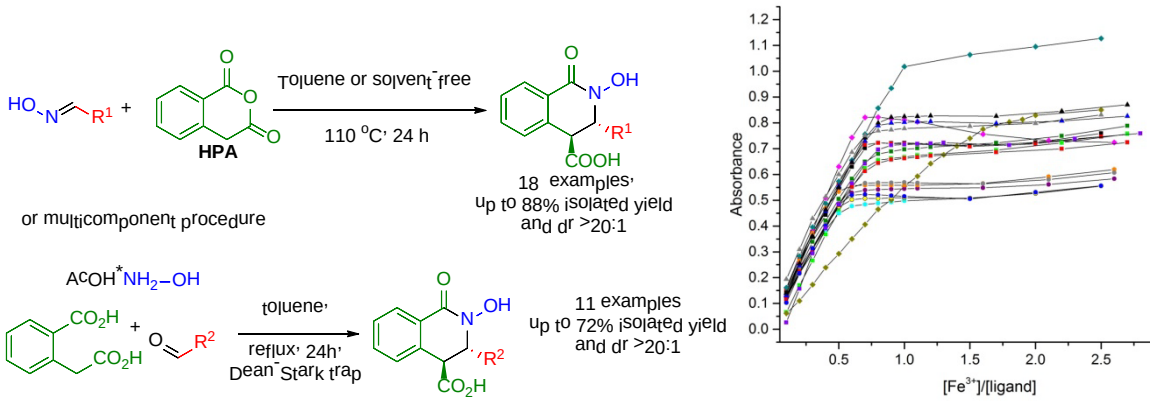
Cyclic hydroxamic acid (*N*-hydroxylactam) motifs are widely displayed in natural products as well as synthetic enzyme inhibitors. Hydroxamic acids have found utility as HIV integrase inhibitors[1], matrix metalloprotease inhibitors[2], histone deacetylase inhibitors[3] and analogs of bacterial siderophores[4]. The latter property was used to develop co-called 'troyan horse' strategy[5] for circumventing drug resistance of bacteria by designing of special carriers for antibiotics. The strategy was also successfully applied for improving fluorescent imaging *in vivo*.

The following study describes a novel practically convenient, approach to *N*-hydroxy tetrahydroisoquinoline (THIQ) acids via formal [2+4] cycloaddition of oximes and homophthalic anhydride (HPA)[6]. Recently a multicomponent procedure of this reaction has been developed in addition. A broad variety of O-unsubstituted and substitued oximes were tested in reaction with HPA, which delivered THIQs in high yields and diastereoselectivity. Some investigated mechanistical aspects of the reaction will be discussed. This new general approach was applied to design more simple and convenient synthesis of biologically active natural compound, 2-*N*-Hydroxy-3,4-dihydroisoqionol-2-one. All products demonstrated strong complexation with iron (III), which was studied spectrophotometrically. Perspectives of using obtained compounds as siderophores and precursors for fluorescent cationic chemosensors will be also discussed.



References:

1 D.C. Pryde *et al.*, *Med. Chem. Commun*. **2013**, *4*, 709–719.
2 Y.-M. Zhang *et al.*,PCT Int. Appl. WO 2008045668; *Chem. Abstr.* **2008**, *148*, 471882.
3 I. Mutule *et al.*, *J. Enzyme Inhib. Med. Chem.* **2015**, *30*, 216-223.
4 I. J. Schalk, M. Hannauer, A. Braud, *Environ. Microbiol.* **2011**, *13*, 2844-2854.
5 A. Gorska, A. Sloderbach, M. P. Marszall, *Trends Pharmacol. Sci.* **2014**, 35, 442-449.
6 O. Bakulina, A. Bannykh, D. Dar'in, M. Krasavin, *Chem.-Eur. J.* **2017**, 23, 17667-17673.
7 Russian Foundation for Basic Research (RFBR) is kindly acknowledged for financial support (project no.18-33-00016)

Poster

Boronic Library Synthesis Using the Acoustic Droplet Ejection Technology

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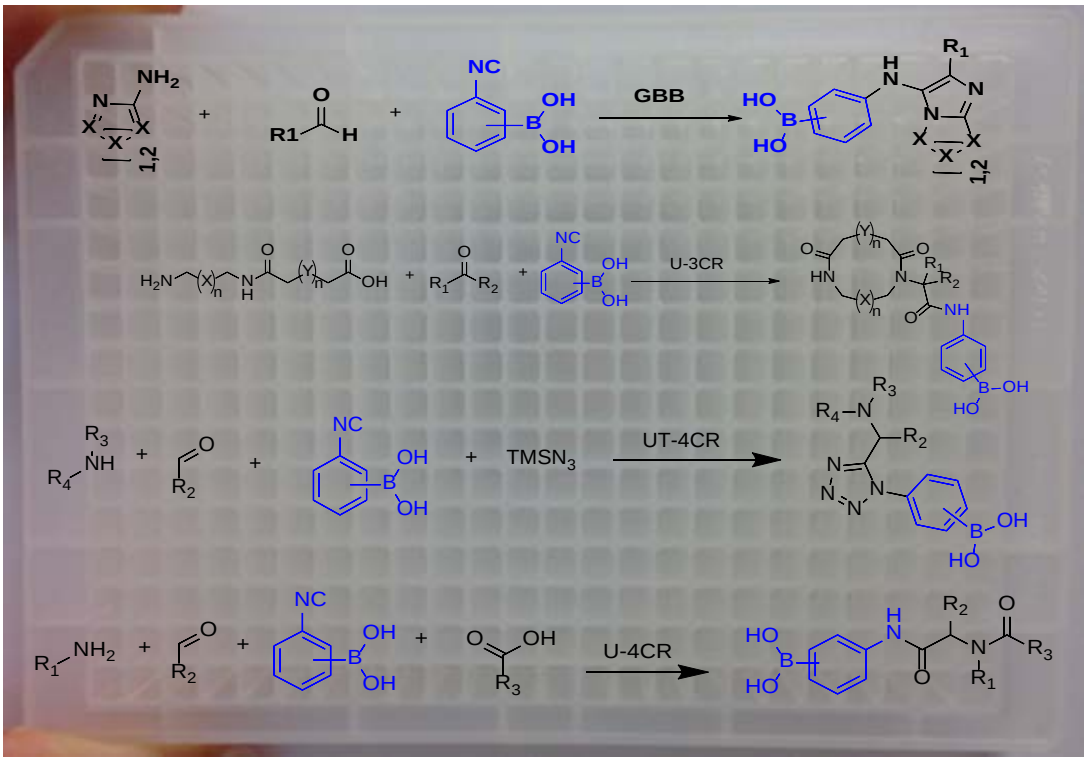
Boronic acids have been known as valuable intermediates in organic chemistry for some time now. More recently, however, they have found applications in medicinal chemistry as well. With the emergence of bortezomib – the first FDA approved a drug that contains a boronic acid moiety- these compounds have started to receive a great deal of attention from the pharmaceutical industry.

Drug Discovery at The Speed of Sound "DDSoS" is the title of a project that aims to leverage automation in order to accelerate the lengthy process of drug design. The project utilizes a state-of-the-art technology called the acoustic droplet ejection (ADE) technology in order to transfer nanoliter-sized droplets of chemicals, dramatically reducing the time required to find new hit compounds.

Our research laboratory is focused on the applications of multicomponent reactions in medicinal chemistry. Mindful of the synthetic importance, as well as the encouraging biological profile of this class of compounds, and as part of the "DDSoS" project, we generated various libraries of phenyl boronic in a 384-well format.

Herein, we discuss how the integration of automation and MCR chemistry has resulted in the generation of large and diverse libraries of compounds with the boronic acid functionality.



References:

1.) R. Ellson, "Picoliter: enabling precise transfer of nanoliter and picoliter volumes". Drug Discovery Today **2002**, 7, 32–34. 2.) J. Comley, "Continued Miniaturisation of Assay Technologies Drives Market for Nanolitre Dispensing". *Drug Discovery World*. Summer **2004**, 43–54. 3.) R. Ellson; M. Mutz; B. Browning; L. Lee; M.F. Miller; R. Papen, "Transfer of Low Nanoliter Volumes between Microwell Plates Using Focused Acoustics – Automation Considerations". *Journal of the Association for Laboratory Automation*, **2003**, *8*, 29–34.

Multi-component and green synthesis of 4-hydroxycoumarin fused triazolopyrimidines using phthalhydrazide-functionalized MCM-41 as a novel catalyst

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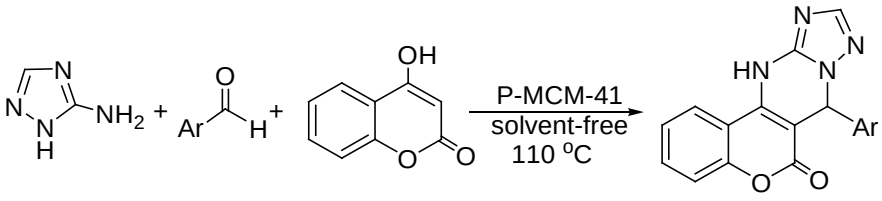
Multi-component reactions (MCRs) as a powerful tool for the rapid introduction and expansion of molecular diversity constitute a highly effective procedure that has many advantages, such as atom economy and facile synthesis of molecules using readily available starting materials.[1] Accordingly, developments of new MCR routes for the generation of heterocycles have attracted much attention in synthetic chemistry.[2]

Triazolopyrimidines are among the most important hybrid heterocycles of pyrimidine as they are structural elements of various bioactive natural products.[3] Also, they are useful compounds for medicinal chemists and starting materials for the synthesis of other fused heterocyclic systems.[4]

As a continuation of our previous work on the applications of heterogeneous catalysts for the development of new synthetic methodologies,[5-7] we here set out to accomplish the following two aims: the preparation of phthalhydrazide-functionalized MCM-41 (P-MCM-41) as a novel mesoporous reusable base catalyst, and study of the applicability of this catalyst for the synthesis of coumarin-fused triazolopyrimidines via a novel three-component reaction of 3- amino-1H-1,2,4-triazole, aromatic aldehydes, and 4-hydroxycoumarin



References:

1 A. Omling, W. Wang, K. Wang, *Chem. Rev*. **2012**, *112*, 3083.
2 A. Váradi, T.C. Palmer, R. N. Dardashti, S. Majumdar, *Molecules* **2016**, *21*, 19.
3 A. S´anchez-Recillas, G. Navarrete-V´azquez, S. Hidalgo- Figueroa, *Eur. J. Med. Chem*. **2014**, *77*, 400.
4 Y. C. Liu, R. Y. Qu, Q. Chen, J. F. Yang, C. Niu, Z. Xi, G. F. Yang, *J. Agric. Food Chem*. **2016**, *64*, 4845.
5 M. Farahi, B. Karami, R. Keshavarz and F. Khosravian, *RSC Adv*. **2017**, *7*, 46644.
6 6. F. Khosravian, B. Karami and M. Farahi, *New J. Chem.* **2017***, 41,* 11584*.*
7 B. Karami, M. Farahi, N. Farmani and H. Mohamadi Tanuraghaj, *New J. Chem*. **2016**, *40*, 1715.

Sequential multicomponent synthesis based on CAL-B catalyzed processes

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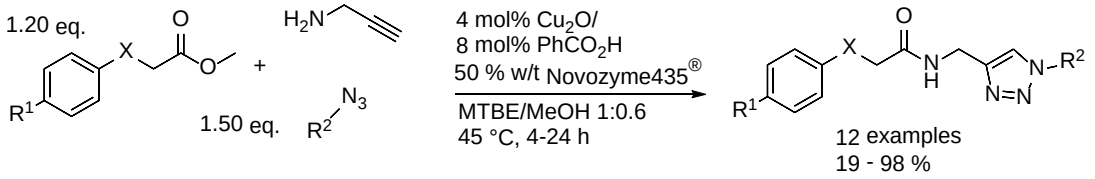
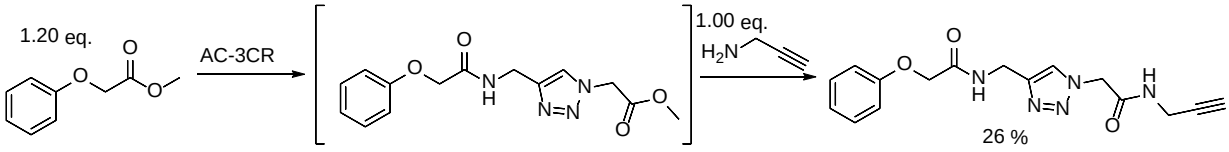
The combination of bio-catalysis and metal-catalysis offers a wide repertoire to new substance classes and opens new pathways to structures, which are hard to access. The turnover rate of enzyme catalyzed reactions is compared to the uncatalyzed reaction bigger by the factor 10^9, that's why enzymes are powerful und well matched biocatalysts.[1] In this work we present the stability and the robustness of the CAL-B. Despite of the presence of methanol, Cu(I)- or Cu(II)-salts, some bases and azides, the CAL-B can carry out an aminolysis. Furthermore the CAL-B can tolerate a large temperature range.[2,3] Based on the work of *S. Hassan*[3] the following pathways and few more were developed.

1. Amidation-*Click*-3-Component-Dominoreaction (*AC-3CDR*)

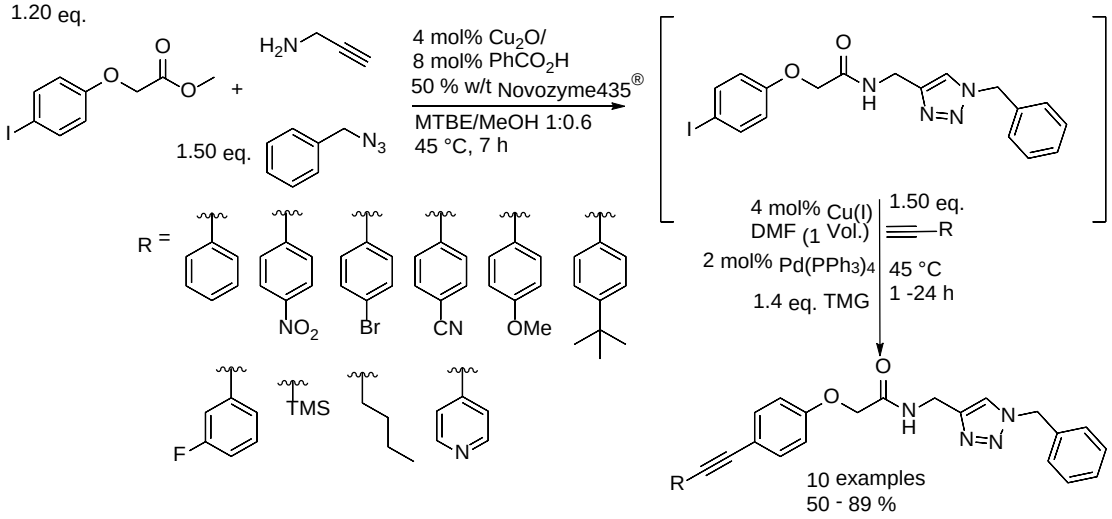
The kinetic of the Dominoreaction shall itemized with the aid of Fluorine-NMR- und HPLC-Study.



2. Amidation-*Click*-Amidation sequence [2]



3. Amidation-*Click-Sonogashira* sequence (*ACS-4CR*)[2]



References:
1 K. Faber, *Biotransformations in* Organic *Chemistry*, Springer, Heidelberg, **2011**.
2 A. Altavilla, *Masterthesis,* **2017**, HHU Düsseldorf.
3 S. Hassan, *Ph.D thesis,* **2014**, HHU Düsseldorf.

V_2O_5/ZrO_2 as an efficient reusable catalyst for the facile, green, one-pot synthesis of novel functionalized 1,4-dihydropyridine derivatives

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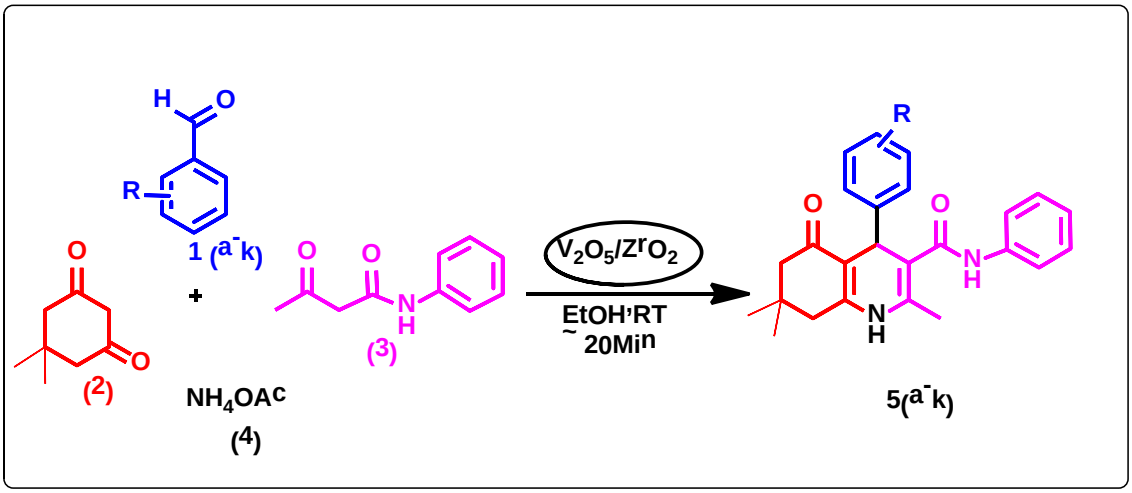
A practical method is designated for the one-pot, multicomponent synthesis of 1,4-dihydropyridine derivatives by cyclo-condensation of aromatic aldehydes, 5,5-dimethyl-1,3-cyclohexanedione, acetoacetanilide and ammonium acetate. Using ethanol as solvent and V_2O_5/ZrO_2 as heterogeneous catalyst, ten novel 1,4-dihydropyridines were synthesized at room temperature (Reaction time<20 min). XRD, TEM, SEM and BET analysis were used to
characterize the catalyst materials. Simple work-up, green solvent, short reaction times, moderate reaction conditions and excellent yields (90–96%) are the attractive features of this novel approach. With no need of chromatographic separation, the reaction product is easily separable in pure form.



References:

1 A. Author, B. Author, *Journal Abbrev.* **year**, *volume*, page.
2 A. Author, B. Author, *Journal Abbrev.* **year**, *volume*, page.
[1] I.E. Wachs, Catal. Today **2005** 100, 79–94.
[2] Z. Guo, B. Liu, Q. Zhang, W. Deng, Y. Wang, Y. Yang, Chem. Soc. Rev. **2014** 43, 3480–3524.

The Groebke-Blackburn-Bienaymé reaction: Two decades later

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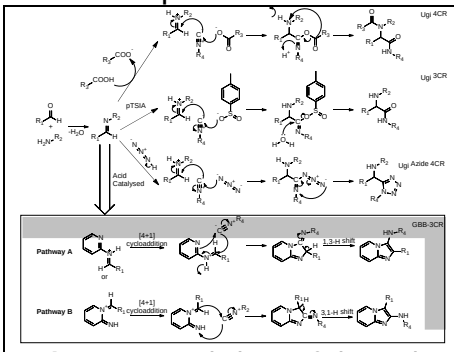
Over the past twenty years, the Groebke, Blackburn, Bienaymè reaction, one of the youngest iMCRs has gained interest and about 50% of the reports were describing the GBB molecules in an application.[1-3] Since 1998 a total of >200 peer reviewed publications and >100 patent applications have been reported exploiting the GBB, with a clear trend of increasing interest, particularly in the last decade. An overview has been made that describes the development of the GBB reaction and alongside a tabular analysis was made to show which exact reagents were reported as one of three components in the GBB reaction.



Scheme 1. *Variations of the Ugi reaction and the Groebke Bienaymé Blackburn reaction. In the GBB mechanism one of the most commonly used amidines; 2-aminopyridine as R_2-group was used in the mechanistic overview to simplify the scheme.*

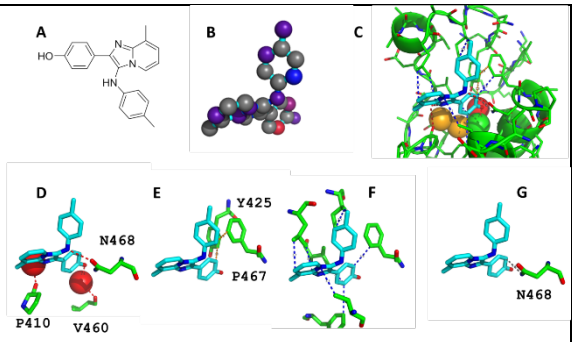


Figure 1. *Step by step analysis for in this example Second Bromodomain (BD2), binding to an GBB imidazopyridine (PDB ID: 5N18).*[4]

The similar mechanism as compared to the Ugi reaction was highlighted (Scheme 1) and the role of the solvent and catalyst were investigated. To a certain degree many conditions, that appear in reports, work well with for GBB in order to get proper yields. Some conditions, however, appear more often than you would expect based upon unbiased screening. This phenomenon and other interesting findings will be discussed and explained.

The well-known scaffold imidazo[1,2*a*]pyridine gained accessibility as it is one of the core structures arising from the GBB reaction. The scaffold is broad applied in many marketed drugs, such as Zolpidem, Minodronic acid, and Miroprofen. These examples however lack the additional 3-aminogroup that is also found in GBB products. For medicinal chemists it is clear that such a group could not be ignored as it will alter the properties of the compounds significantly. To better illustrate the applications of GBB compounds in a biological perspective, an overview was made with relevant examples for a large variety of targets. Moreover, a patent analysis was included in the overview. A few examples that were reported as co-crystals in their target proteins were subjected to a more in depth analysis of their mode of binding (figure 1).

[1] K. Groebke, L. Weber, F. Mehlin, *Synlett* **1998**, 661-663.
[2] C. Blackburn, B. Guan, P. Fleming, K. Shiosaki, S. Tsai, *Tetrahedron Lett.* **1998**, *39*, 3635-3638.
[3] H. Bienayme, K. Bouzid, *Angew. Chem., Int. Ed.* **1998**, *37*, 2234-2237.
[4] F. Mietton, E. Ferri, M. Champleboux, N. Zala, D. Maubon, Y. Zhou, M. Harbut, D. Spittler, C. Garnaud, M. Courcon, M. Chauvel, C. d'Enfert, B. A. Kashemirov, M. Hull, M. Cornet, C. E. McKenna, J. Govin, C. Petosa, *Nat Commun* **2017**, *8*, 15482.

VICARIOUS NUCLEOPHILIC SUBSTITUTION IN NITROINDAZOLES

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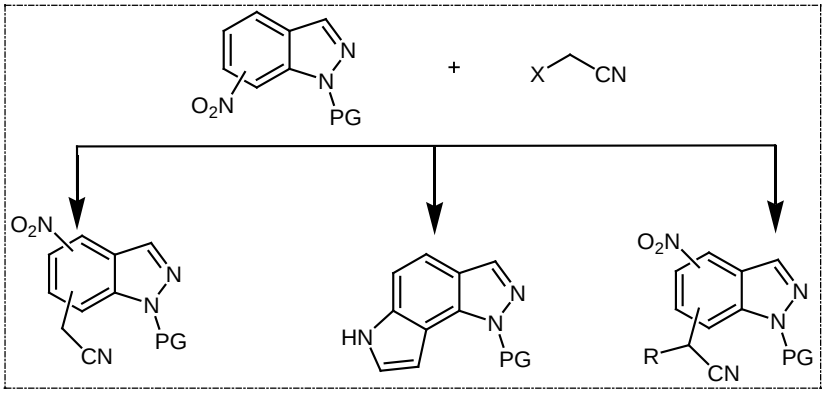
Vicarious Nucleophilic Substitution, VNS, of hydrogen provides a convenient method to introduce functional groups into aromatic and heterocyclic rings [**1-4].** This two-step reaction proceeds via addition of carbanion containing leaving groups X at the carbanionic center to the nitroaromatic ring followed by the base-induced β-elimination of HX from intermediate σ-adducts. The products of VNS reactions are key intermediates in the synthesis of useful and new heterocyclic compounds.

Indazole core is the best skeleton to develop anticancer agents. It is recognized to be a highly effective pharmacophore in medicinal chemistry as well as being the core of important nitrogen-containing heterocycles that show a broad range of biological activities **[5-11]**.

Our contribution is to develop potent and selective anticancer agents. So, we investigated the VNS reaction on nitroindazoles in mild conditions. We obtained new substituted indazoles as precursors to synthesis pharmacologically active polyheterocyclic compounds.



Scheme

References

[1] Czaban-Jóźwiak, J., Loska, R., Mąkosza, M., *J. Org. Chem.*, **2016,** 81, 11751. **[2]** Sakowicz, A., Loska, R.; Mąkosza, M. Synlett, **2016,** 27, 2443. **[3]** Makosza, M., *Chem. Eur. J.*, **2014**, 20, 1. **[4]** Mąkosza, M., Wojciechowski, K., *Chem. Heterocycl. Compd.*, **2015,** 51, 210. **[5]** Cerecetto, H., Gerpe, A., Gonzalez, M., Aran, V. J., de Ocariz, C. O. *Mini-Rev Med Chem.*, **2005,** 5, 869. **[6]** (a) Cerecetto, H.; Gerpe, A.; Gonzalez, M.; Aran, V. J.; de Ocariz, C. O. Mini-Rev Med Chem 2005, 5, 869-878; (b) Gaikwad, D. D.; Chapolikar, A. D.; Devkate, C. G.; Warad, K. D.; Tayade, A. P.; Pawar, R. P.; Domb, A. J. Eur. J. Med Chem., **2015**, 90, 707. **[6]** Jennings, A.; Tennant, M. J ChemInfo Model **2007**, 47, 1829–1838. **[7]** Gaikwad, D. D., Chapolikar, A. D., Devkate, C. G., Warad, K. D., Tayade, A. P., Pawar, R. P., Domb, A. *J. Eur. J. Med. Chem*., **2015,** 90, 707. **[8]** El Ghozlani, M., Chicha, H., Abbassi, N., Chigr, M., El Ammari, L., Saadi, M., Spinelli, D., Rakib, E. M., Tetrahedron Lett., **2016,** 57, 113. **[9]** Abbassi, N., Rakib, E. M., Chicha, H., Bouissane, L., Hannioui, A., Aiello, C., Gangemi, R., Castagnola, P., Rosano, C., Viale, M. *Arch. Pharm. Chem. Life Sci*. **2014**, 347, 423. **[10]** Abbassi, N., Chicha, H., Rakib, E. M.; Hannioui, A.; Alaoui, M.; Hajjaji, A.; Geffken, D.; Aiello, C.; Gangemi, R.; Rosano, C.; Viale, M. *Eur. J. Med. Chem.*, **2012,** 57, 240. **[11]** Kouakou, A., Micheletti, G., Boga, C., Calvaresi, M., Chicha, H., Franchi, P., Guadagnini, L., Lucarini, M., Rakib, E. M., Spinelli, D., Tonelli, D., *Curr. Org. Chem*. **2015**, 19, 1526-1537.

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Consecutive Alkynylation-Michael Addition-Cyclocondensation (AMAC) Multicomponent Syntheses of α-Pyrones and α-Pyridones

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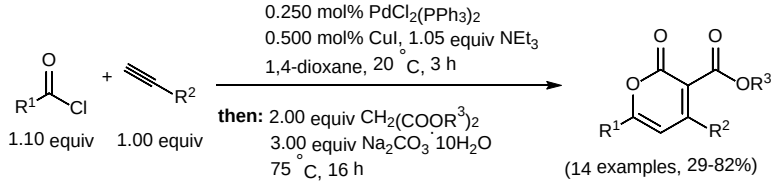
α-Pyrones are six-membered unsaturated lactones[1] and they are key motifs in many natural products, which have been isolated from various animals, plants, marine organisms, bacteria, fungi, and insects. These natural products exhibit a wide range of biological activities, including anti-fungal, cytotoxic, neurotoxic and phytotoxic properties.[2] α-Pyrones can also be applied for the synthesis of more complex molecules due to their diene character.[3] The 1,4-addition of malonic esters to alkynones represents an interesting access.[4]
The aim of the present work is to prepare the α-pyrone moiety *via* a consecutive-three-component synthesis without isolation of the intermediate alkynone. The sequence starts with a *Sonogashira* coupling of a terminal alkyne and an acid chloride. The α-pyrones scaffold is formed by the reaction of dialkyl malonate and $Na_2CO_3 \cdot 10H_2O$. Due to its modular nature the reaction sequence offers quick access to a broad variety of substituted α-pyrones by variation of the terminal alkyne and acid chloride. Electron-donating as well as -accepting substituents are well tolerated.[5]



Scheme 1: Three-component synthesis of α-pyrones.

By concatening the ammonolysis of the α-pyrones an alkynylation-Michael addition-cyclocondensation-ammonolysis (AMACA) synthesis of α-pyridones can be conceived. α-Pyridone products with and without ester functionality are obtained.

Literature:

[1] P. J. Brogden, C. D. Gabbutt, J. D. Hepworth, *Comprehensive Heterocyclic Chemistry* **1984**, *3*, 573-645.

[2] a) J. S. Lee, *Mar. Drugs* **2015**, *13*, 1581-1620. b) G. P. McGlacken, I. J. S. Fairlamb, *Nat. Prod. Rep*. **2005**, *22*, 369-385.

[3] K. Afarinkia, V. Vinader, *Science of Synthesis* **2003**, *14*, 275.

[4] Z. G. Specht, D. B. Grotjahn, C. E. Moore, A. L. Rheingold, *Organometallics* **2013**, *32*, 6400-6409.

[5] N. Breuer, T. J. J. Müller *Synthesis* **2018**, manuscript accepted

Novel Organic Tetraisocyanide: 1,3-Diisocyano-2,2-bis(isocyanomethyl)propane Synthesis and Utilization in the Ugi-4CR

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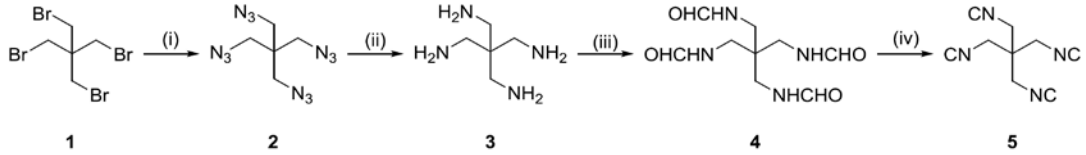
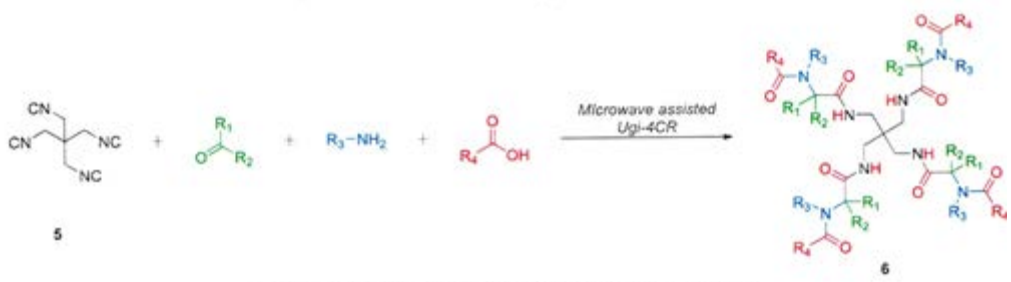
Organic tetraisocyanides are an extremely rare species of isocyanides. In fact, there are only three reports of synthesized organic tetraisocyanides to the extent of our knowledge.[1–3] Nonetheless, bearing four isocyanide groups in one molecule represents an attractive starting point for diverse applications, for example in drug discovery or materials science. As far as reported, the use of this tetraisocyanides, based on the outstanding complexation ability of isocyanides, was exclusively as ligands in transition metal complexes, e.g. with gold, tungsten and copper. [1–4]
Hereby, we report the first successful synthesis of a novel tetraisocyanide (**Scheme 1**, **5**). We were able to synthesize the aliphatic, symmetrical tetraisocyanide **5** in a four step synthetic route starting from pentaerythritol tetrabromide (**1**), a commercially available and cheap starting material. This synthetic route allowed us to synthesize the tetraisocyanide **5** in gram-scale in overall fair yields. The synthesized tetraisocyanide is highly stable and solid at room temperature.



Scheme 1: 4-step synthetic route to 1,3-diisocyano-2,2-bis(isocyanomethyl)propane (5), (i) NaN_3, DMF, 80°C, 24h; (ii) H_2-Pd/C, 40°C, 4h; (iii) Ethyl formate, 60°C, 18h; (iv) $POCl_3$, DCM, -7°C-rt,7h.

The first two synthesis steps are based on the work of W. Hayes *et al*.[5], while the formylation and subsequent dehydration were accomplished by protocols developed in our working group resulting in the tetraisocyanide **5**. Furthermore growing crystals of the formamide **4** and the tetraisocyanide **5** was accomplished; the corresponding structures were verified by X-ray crystallographic analysis. With the tetraisocyanide in hands, we developed a method to implement a fourfold Ugi-4CR (**Scheme 2**).



Scheme 2: Reaction of the tetraisocyanide 5 in an Ugi-4CR.

Using microwave assisted heating under catalyst free conditions led to several compounds consisting of the unique core structure **6.** Validation by NMR spectroscopy and mass spectrometry verified the reaction of all four isocyanide groups in the performed Ugi-4CR. Furthermore, the implementation of a microwave assisted Ugi-4CR resulted in the advantage of a short reaction time of only two hours. Besides, preliminary positive results using the tetraisocyanide **5** in a Passerini-3CR enhanced our pursuit for additional research.
Thus, this tetraisocyanide **5** can represent the starting point for many exciting compounds, for example multivalent drug candidates. By now, we are exploring further application of this novel tetraisocyanide in IMCR to achieve a wider spectrum of its usage and discover novel compounds with unique structures and properties.

1. Y. Ito, K. Kobayashi, T. Saegusa, *J. Organomet. Chem.* **1986**, *303*, 301–308;
2. M. G. Hill, M. C. Comstock, K. R. Mann, *J. Org. Chem.* **1990**, 4950–4951.
3. J. Gagnon, M. Drouin, P. D. Harvey, *Inorg. Chem.* **2001**, *40*, 6052–6056.
4. M. Toriyama, T. R. Maher, T. C. Holovics, K. Vanka, V. W. Day, C. L. Berrie, W. H. Thompson, M. V. Barybin, *Inorg. Chem.* **2008**, *47*, 3284–3291.
5. W. Hayes, H. M. I. Osborn, S. D. Osborne, R. A. Rastall, B. Romagnoli, *Tetrahedron,* **2003**, *59*, 7983–7996.

MCR scaffolds as synthons for the development of PET radiotracers

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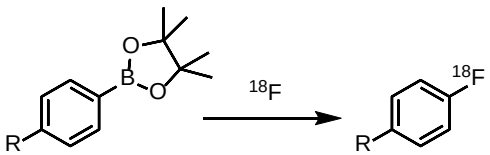
In nuclear medicine and molecular imaging, positron emission tomography (PET) represents a great progress in the clinical development of drugs and diagnostics due to its unique capacity to detect, with high sensitivity, ranges of analytes, in vitro or in vivo, that can go down to the picomolar scale. This imaging technique greatly relies on the development of molecules of interest which incorporate a β^+-emitter element (e.g. ^{15}O, ^{13}N, ^{11}C, ^{18}F…) with very short physical half-lives ranging from 2-110 min. Nonetheless, one of the many challenges is the timely and effective development of molecules (synthons) that can be promptly radiolabeled by appropriately efficient methods. The synthesis of numerous drugs and small drug-like compounds with high structural diversity have already shown to benefit from convergent multicomponent strategies.[1] MCRs also provide a quicker, versatile and proficient way to generate vast libraries of small organic molecules from communal intermediate backbones, allowing a time-efficient approach to investigate how small changes in the overall scaffold may influence functional, biological or pharmacological activity.
The combination of PET radiolabeling with MCR synthesis of biologically active compounds has the potential to greatly simplify radioanalytical and imaging based analyses. It can positively influence the design, synthesis and characterization of active compounds, evaluate their toxicity, PK/PD properties and ultimately shorten the temporal gap among the different clinical trial phases.

Herein, we present a proof of concept study where several structurally different drug-like isocyanide-based MCR scaffolds (e.g. arenes, β-lactam, tetrazole, oxazole) were synthesized to specifically contain a pinacol-derived aryl boronic ester moiety, and used to produce their [^{18}F]fluorinated counterparts. These synthons were used since Cu-mediated oxidative [^{18}F]fluorination of arylboronic acid pinacol ester derivatives tolerate electron-poor and electron-rich arenes with various functional groups.[2]



In summary, reproducible radiochemical conversion yields from 15% to 76% with short reaction times (20 to 30 min.), depending on the scaffolds, were achieved, demonstrating the feasibility of the [^{18}F]fluorination of biologically active molecules synthesized via MCR. The developed method shows the potential to apply [^{18}F]fluorination in line with MCR and also has a latent possibility of incorporating the radiolabeling step in a later stage of this convergent “one-pot” synthesis strategy. Finally, a copper(I)-catalyzed [^{11}C]carboxylation of the boronic acid esters is also a further perspective, which may expand the variability of options beyond fluorine-containing drugs.[3]

References:

1 T. Zarganes-Tzitzikas, A. Dömling, *Org. Chem. Front.* **2014**, 1(7):834-837
2 M. Tredwell, S.M. Preshlock, N.J. Taylor, S. Gruber, M. Huiban, J. Passchier, J. Mercier, C. Génicot, V. Gouverneur, *Angew. Chem. Int. Ed.* **2014**, 53:7751–7755.
3 P.J. Riss, S. Lu, S. Telu, F.I. Aigbirhro, V.W. Pike, *Angew. Chem. Int. Ed.* 2012, 51:2698-2702.

Consecutive One-Pot Synthesis of 3,4,5-Triarylated Isoxazoles Employing Pd-catalyzed C-H-activation

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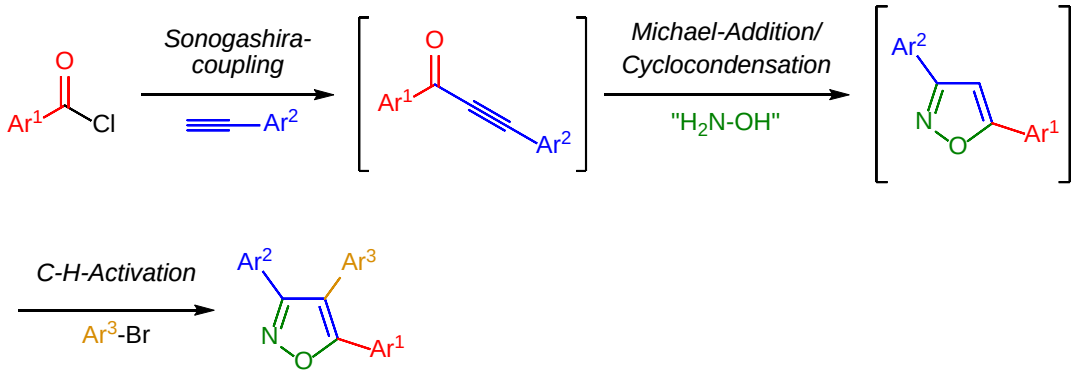
Compounds containing the isoxazole motif often exhibit interesting biological activities[1] and are employed as building blocks in materials science.[2]

Therefore, we have developed a synthetic protocol consisting of a four-component reaction that employs a consecutive palladium-catalyzed C-H-activation step. This novel *coupling-addition-cyclocondensation-C-H-activation* sequence commences with catalytic alkynone formation[3] and cyclocondensation[4] and concludes with C-H-arylation giving access to 3,4,5-triarylated isoxazoles (Scheme 1).



References:

1 D. Giomi, F. M. Cordero, F. Machetti, In *Comprehensive Heterocyclic Chemistry III*, Vol. 4 (Eds.: A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven, R. J. K. Taylor), Elsevier, Oxford **2008**, pp. 365–485.

2 a) M. Tanaka, T. Haino, K. Ideta, K. Kubo, A. Mori, Y. Fukazawa, *Tetrahedron* **2007**, *63*, 652–665; b) A. A. Vieira, F. R. Bryk, G. Conte, A. J. Bortoluzzi, H. Gallardo, *Tetrahedron Lett.* **2009**, *50*, 905–908.

3 a) A. S. Karpov, T. J. J. Müller, *Synthesis* **2003**, 2815–2826. b) D. M. D'Souza, T. J. J. Müller, *Nat. Protoc.* **2008**, *3*, 1660-1665.

4 H.-L. Liu, Z.-F. Geng, S.-Y. Zhang, J. Han, *Heterocycles* **2014**, *89*, 1221–1227.

Some new perspectives in silyl-Prins multicomponent reactions

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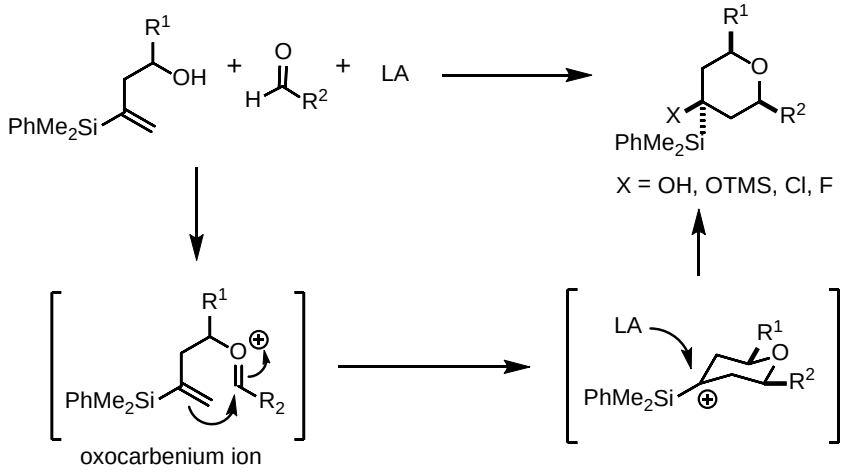
Prins cyclization has emerged as an efficient method for the synthesis of tetrahydropyrans in the last decades.[1] In this reaction an aldehyde and a homoallylic alcohol form an oxocarbenium ion in the presence of a Lewis or protonic acid. A variant of the general process is the silyl-Prins methodology.[2] It usually provides higher selectivity and fewer competitive oxo-Cope rearrangements. Generally, it consists in the use of a trimethylsilyl group attached to the double bond and proceeds with loss of this silyl group, leading to dihydropyrans.[3]
To the best of our knowledge, there is only one isolated example of a multicomponent silyl-Prins cyclization, in which the Lewis acid transfers part of its structure to the final product.[4] Thus, we decided to develop similar procedures to try to reproduce such a result. By using the more robust $PhMe_2Si$ group, we were able to perform different types of multicomponent reactions, in which the intermediate maintains the silyl group and captures part of the structure of the Lewis acid. In this presentation we will discuss the mechanism of this multicomponent reaction, as well as the influence of the acid in the process.



References:
1 a) M.P. Isidro, Y. Miguel, *Curr. Org. Chem.* **2007**, *11*, 925. b) C. Olier, M. Kaafarani, S. Gastaldi, M.P. Bertrand, *Tetrahedron* **2010**, *66*, 413. c) X. Han, G. Peh, P.E. Floreancig, *Eur. J. Org. Chem.* **2013**, *2013*, 1193.
2 A.P. Dobbs, S. Martinovic, *Tetrahedron Lett.* **2002**, *43*, 7055.
3 a) Y. Lian, R.B. Hinkle, *J. Org. Chem.* **2006**, *71*, 7071. b) Z. Chu, K. Wang, L. Gao, Z. Song, *Chem. Comm.* **2017**, *53*, 3078.
4 L.E. Overman, A. Castañeda, T.A. Blumenkopf *J. Am. Chem. Soc.* **1986**, *108*, 1304.

Synthesis of Meriolin Derivates via Masuda-Suzuki Sequence

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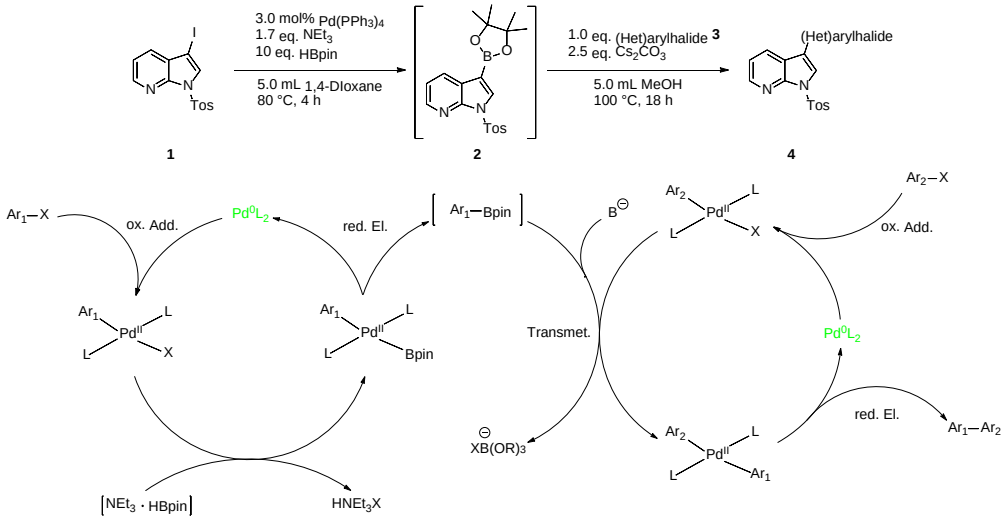
Introduction

A variety of marine alkaloids, such as meridianins[1] and variolins,[2] consist of an indole or a 7-azaindole core. Together with a 2-aminopyridinyl moiety in 3-position, this structural element becomes a lead structure for the inhibition of kinases. In principle, 3-heteroaryl substituted 7-azaindoles are potent hinge binders in kinases. Various 7-azaindole based amino pyrimidines and amino pyridines have been shown to selectively inhibit serine-threonine kinases at lower nanomolar IC_{50}-values. In some cases also cocrystallized ligands with kinase domains of signaling cascade proteins (e.g. PDK1) were obtained.[3]

Masuda-Suzuki Sequence

With the development of the Masuda-Suzuki sequence it is now possible to create substance libraries of 3- (hetero)aryl substituted 7-azaindoles (**4**) easily and efficiently.[4] The iodide (**1**) can be converted in the presence of 3 mol% $Pd(PPh_3)_4$ with pinacolborane and triethylamine as a base to the corresponding pinacolyl ester (**2**). After successful transformation, the addition of methanol is sufficient to scavenge the excess of pinacolborane. Subsequently, in the same reaction vessel commercially available (hetero)aryl halides (**3**) and cesium carbonate as a base are added to further transform the formed boronic ester under Suzuki coupling conditions without further addition of catalyst. The protecting group remains intact in the sequence and can be selectively cleaved in a third step by addition of sodium hydroxide (Scheme 1).



Scheme1: Formation of a carbon-carbon bond between two (hetero)aryl halides via Masuda-Suzuki sequence.

Conclusion

The Masuda-borylation-Suzuki-coupling sequence is a reliable methodology for easily accessing a broad spectrum of novel active agents in a one-pot fashion. Moreover, a highly diversity-oriented synthesis by simply changing the halides can be readily achieved.

References:

[1] M. D. Lebar B. J. Baker, *Aust. J. Chem.* **2010**, *63*, 862-866; A. M. Seldes, M. F. R. Brasco, L. H. Franco, J. A. Palermo, *Nat. Prod. Res*. **2007**, *21*, 555-563; L. H. Franco, E. Bal de Kier Joff´e, L. Puricelli, M. Tatian, A. M. Seldes, J. A. Palermo, *J. Nat. Prod.* **1998**, *61*, 1130-1132.

[2] N. B. Perry, L. Ettouati, M. Litaudon, J. W. Blunt, M. H. G. Munro, S. Parkin, H. Hope, *Tetrahedron* **1994**, *50*, 3987-3392; G. Trimurtulu, D. J. Faulkner, N. B. Perry, L. Ettouati, M. Litaudon, J. W. Blunt, M. H. G. Munro, G. B. Jameson, *Tetrahedron* **1994**, *50*, 3993-4000.

[3] A. Echalier, K. Bettayeb, Y. Ferandin, O. Lozach, M. Clément, A. Valette, F. Liger, B. Marquet, J. C. Morris, J. A. Endicott, B. Joseph, L. Meijer, *J. Med. Chem.* **2008**, *51*, 737-751.

[4] E. Merkul, E. Schäfer, T. J. J. Müller, *Org. Biomol. Chem.* **2011**, *9*, 3139-3141.

Ugi-Chembricks: Designable multimacrocycles in three steps

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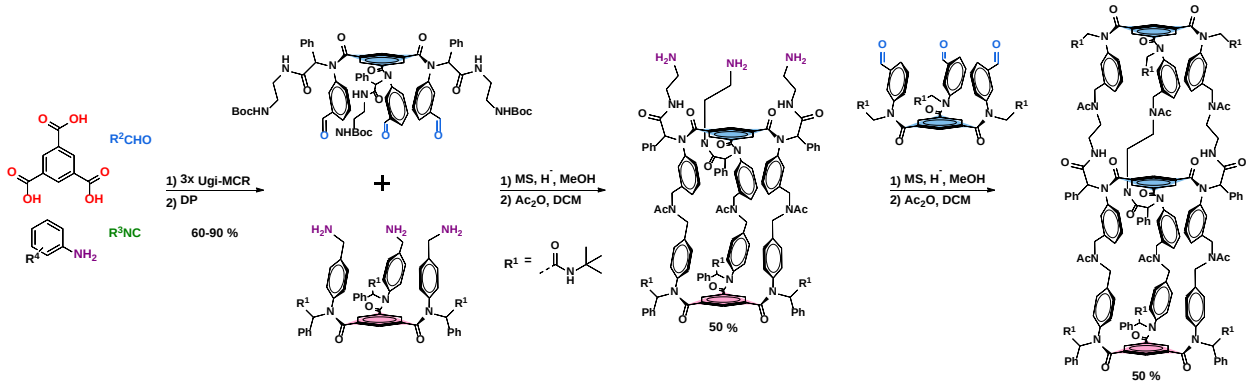
A new approach towards molecular cages, built bottom-up in three steps, is presented. Herein, the advantages of the Ugi-4CR and dynamic covalent chemistry (DCC) are combined to yield defined molecular cages[1]. First, Ugi-chembricks are produced via Ugi-4CR in high yields from bulk chemicals. The chembricks show s-*cis* configuration of the *N*-alkylated amide bonds and preferred *syn*-conformation if trimesic acid is used as starter in the triple Ugi-4CR. Second, the combination of two deprotected chembricks is highly favored due to this preconformation, and molecular cages can easily be obtained in good yields without special preconditions. Two suitable chembricks are mixed in MeOH and after formation of the imine cage, reduction, and acetylation, a well-defined molecular cage is isolated. By making use of further connection points, even bigger molecular cages can be synthesized in a stepwise approach, by adding another chembrick with directional groups (see figure). While in the near future DCC might still be an important tool to produce covalent organic frameworks and porous organic cages from rigid starting materials[2], the new method described here will enable everyone with a modest lab to construct diverse Ugi-chembricks and defined molecular cages thereof, which can be optimized by changing starters of the Ugi-4CR.



References:

1 L. A. Wessjohann, O. Kreye, D. G. Rivera, *Angew. Chem.* **2017**, *129*, 3555; D. G. Rivera, L. A. Wessjohann, *J. Am. Chem. Soc.* **2009**, *131*, 3721.
2 F. Beuerle, B. Gole, *Angew. Chem. Int. Ed.* **2018**, *57*, 4850.

Evolving Artificial Macrocyclic Chemical Space by applying MCR chemistry

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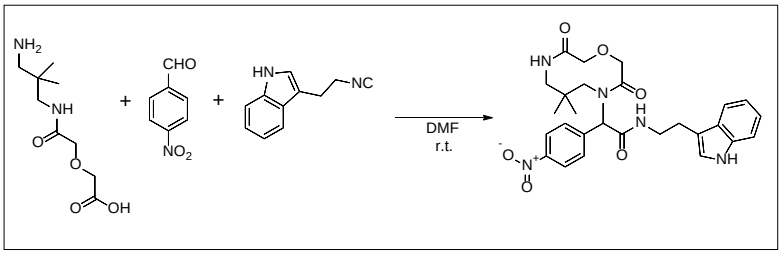
Macrocycles are molecules containing 12-membered or larger rings and they have a great abundance in nature. However in medicinal chemistry, artificial macrocycles are still largely unexplored and underused. Several reasons have led to this situation, including their synthetic challenge due to complex sequential synthesis and also their seemingly orally bio-unavailable and drug-unlike shortages. In recent years, several macrocyclic drugs have been successfully put in the market, in addition, it is found that macrocycles have great potential in challenging protein targets while relatively small molecules cannot accomplish this tough task. Due to these facts, now macrocycles are gaining an increasing focus both from synthetic and medicinal fields. [1]
Regarding synthetic aspect, many new synthetic methods have been developed, yet most of them focus on sequential multistep synthesis which are indeed time-consuming, largely lower the atom economy and also involve a lot of uncertainty due to lengthy synthetic steps. Herein, MCR chemistry will show its unparalleled advantages in constructing macrocycles with different sizes and shapes by applying different types of MCR reactions such as Ugi-4C reaction, Passerini reaction and GBB reaction. [2]



References:

1 a) Driggers E M, Hale S P, Lee J, et al. *Nat. Rev. Drug Discov.***, 2008**, *7*(7): 608-624; b) Mallinson J,Collins I. *Future Med. Chem*. **2012**, *4*(11): 1409-1438; c) Marsault E, Peterson M L. *J. Med. Chem.***, 2011**, *54*(7): 1961-2004.
2 a) Madhavachary R, Abdelraheem EM, Rossetti A, Twarda-Clapa A, Musielak B, Kurpiewska K, Kalinowska-Tłuścik J, Holak TA, Dömling A. *Angew. Chem. Int. Ed.* **2017**,*56*(36):10725-10729; b) Abdelraheem EM, Kurpiewska K, Kalinowska-Tłuścik J, Dömling A. *J. Org. Chem*. **2016**,*81*(19):8789-8795; c) Liao GP, Abdelraheem EM, Neochoritis CG, Kurpiewska K, Kalinowska-Tłuścik J, McGowan DC, Dömling A. *Org. Lett,* **2015**,*17*(20):4980-4983.

One-Pot Synthesis and Photophysical Properties of 5,8-Disubstituted Psoralens

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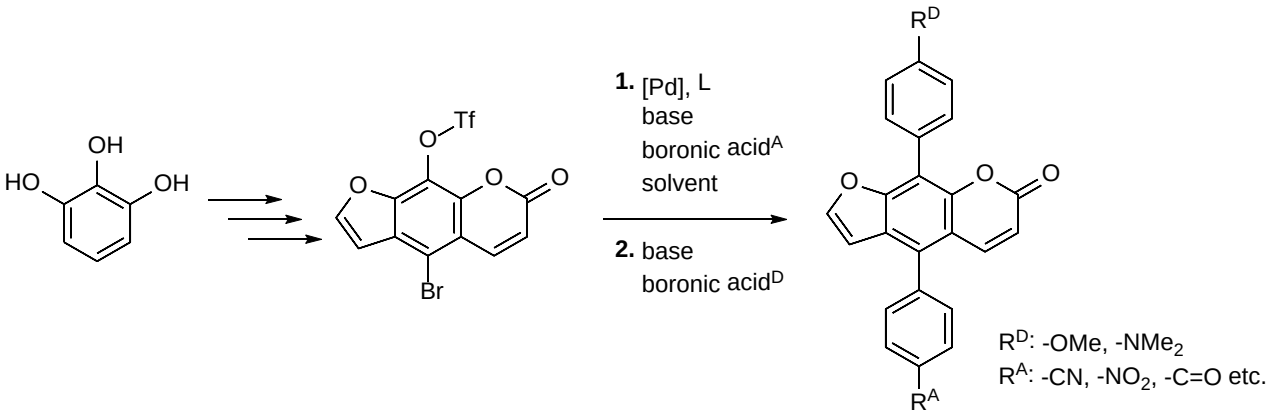
Psoralens are DNA intercalators and can undergo photoreactions causing hindrance of DNA replication and transcription. With this respect the PUVA (psoralen + UV-A-light) therapy offers advantages in treatment of cancer and several skin diseases.[1,2] To study the crosslinking photocycloadditions with the DNA the electronic structure of the psoralens must be controlled and optimized.

A diversity-oriented approach leads to a new generation of 8-donor-5-acceptor substituted psoralens. Simultaneously the structure-property relationships concerning the photoreactivity of psoralens with DNA are investigated. Subsequently to a preparative route starting with commercially available pyrogallol the 8-(5-bromo)psoralene trifluoromethanesulfonate as the pivotal coupling partner could be generated.[3,4]
Hence, 5-acceptor-8-donor substituted psoralens can be synthesized by a selective *Suzuki-Miyaura* cross-coupling sequence. Introduction of donor groups at the 8-position should lead to a bathochromic shift of the absorption bands. Furthermore, substituted psoralenes show fluorescence in solution and in the solid state.



Scheme 1: Preparative route of 5-acceptor-8-donor substituted psoralens.

References:
[1] J. W. Tessman, S. T. Isaacs, J. E. Hearst, *Biochemistry* **1985,** *24,* 1669-1676.
[2] T. F. Anderson, J. J. Voorhees, *Annu. Rev. Pharmacol. Toxicol.* **1980,** *20,* 235-257. [3] R. A. Leão, P. F. de Moraes, M. C. Pedro, *Blucher Chemistry Proceedings* **2013,** *1,* 72-72.
[4] J. Timonen, K. Vuolteenaho, T. Leppänen, R. Nieminen, E. Moilanen, P. Aulaskari, J. Jänis, *J. Heterocycl. Chem.* **2015,** *52,* 1286-1295.

Multicomponent synthesis of steroid analogs with complex side chains as nuclear receptor ligands in nematodes and mammalians

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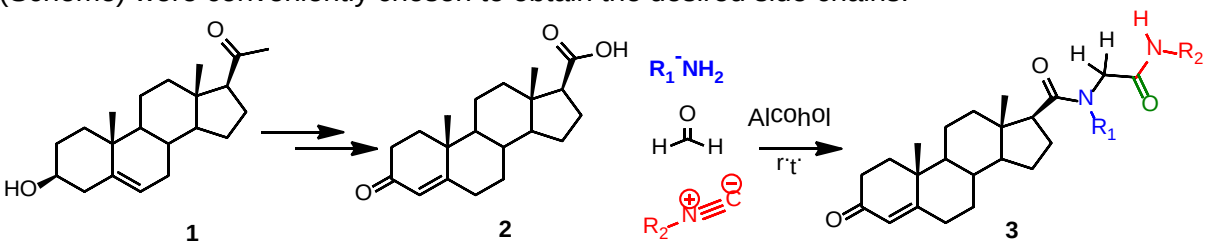
Multicomponent reactions offer many advantages over traditional synthetic approaches in drug discovery. In particular, the Ugi four-component reaction (U-4CR) allows to generate chemical libraries with enhanced structural complexity and diversity.[1] In this work we describe the synthesis of a small set of steroids of general structure **3** having highly diverse side chains, which were constructed using a traditional U-4CR (Scheme).
The acidic component of the U-4CR, steroid **2**, was obtained from pregnenolone **1** in three steps.[2–4] In addition to formaldehyde, various amines (R_1-NH_2) and isonitriles (R_2-NC) (Scheme) were conveniently chosen to obtain the desired side chains.



Finally, these compounds were used for studies involving their interactions (as agonist or antagonist) with two nuclear receptors. On the one hand, we chose the DAF-12 nuclear receptor of the nematode *C. elegans.* The endogenous steroidal ligand of DAF-12 (dafachronic acid) modulates the developmental status along the lifespan of this organism. As this receptor bears high homology to other nuclear receptors found in mammals, it is usually considered a good model for the discovery of new compounds with potential clinical use. On the other hand, the compound library was evaluated as ligands of the progesterone receptor, a prototype of a more evolved nuclear receptor. Comparing the differential activities of the compounds in both systems, an attempt at assessing the promiscuity of the nuclear receptors as steroid sensors is discussed.

References:

1 A. Dömling, I. Ugi, *Angew. Chemie* **2000**, *39*, 3168–3210.
2 W. Zeinyeh, Z. Mahiout, S. Radix, T. Lomberget, A. Dumoulin, R. Barret, C. Grenot, L. Rocheblave, E. L. Matera, C. Dumontet, et al., *Steroids* **2012**, *77*, 1177–1191.
3 J. Rey, T. J. C. O'Riordan, H. Hu, J. P. Snyder, A. J. P. White, A. G. M. Barrett, *European J. Org. Chem.* **2012**, *1*, 3781–3794.
4 F. K. Yoshimoto, M. C. Desilets, R. J. Auchus, *J. Steroid Biochem. Mol. Biol.* **2012**, *128*, 38–50.

Diversity Oriented Synthesis of Novel Aza-analogues of (±)-Nuevamine, (±)-Lennoxamine and Magallanesine

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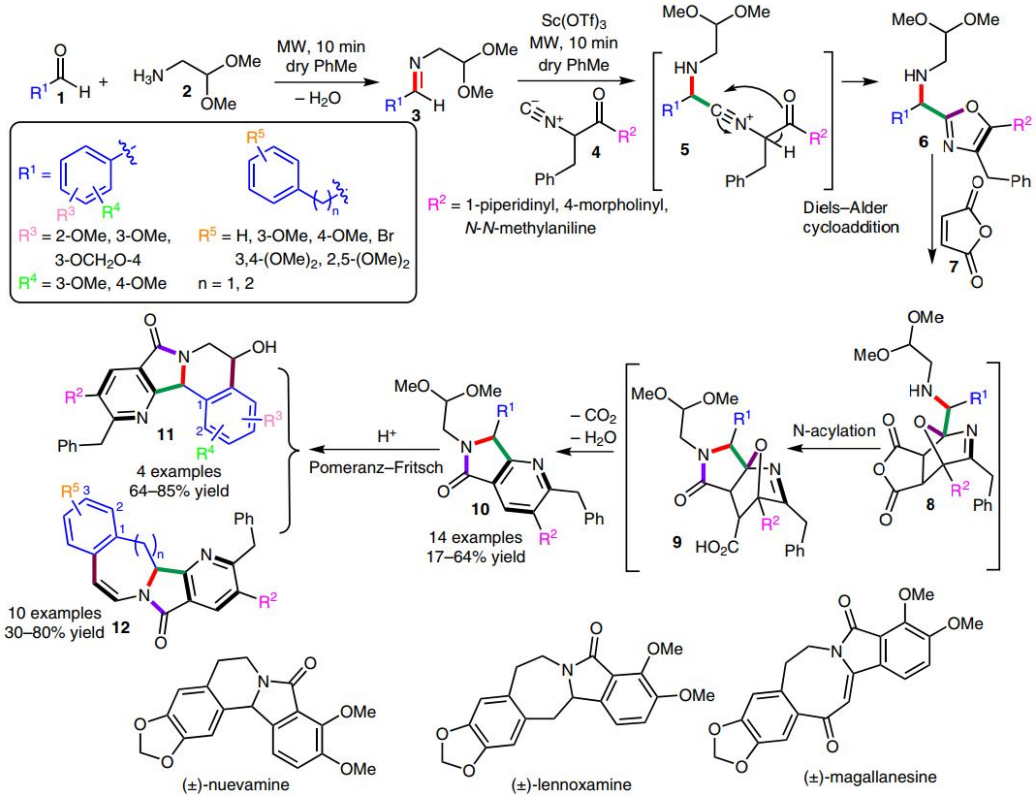
A rapid and efficient synthesis of a series of (±)-Nuevamine, (±)-Lennoxamine and Magallanesine aza-analogues is described. The synthetic strategy involves an Ugi-3CR coupled to two further cyclization processes: *i)* a cascade (aza Diels-Alder cycloaddition/*N*-acylation/aromatization), and *ii)* an intramolecular Pomeranz-Fritsch annulation. The variation of chain-size in the aldehyde moiety provided structural diversity in only two operational reaction steps yielding 30 to 85% overall.[1] This novel synthetic strategy is in line with our recent publications describing the use of Ugi-3CRs coupled to a variety of further cyclization methods toward novel polyheterocyclic pyrrolo[3,4-*b*]pyridin-5-ones,[2] **Scheme 1**.



Scheme 1. Diversity Oriented Synthesis-based strategy toward novel analogues of natural products (taken from *Synfacts* **2017**, *13,* 362 (Snieckus Innovation), DOI: 10.1055/s-0036-1590199).

References:

1 O. Vázquez-Vera, J.S. Sánchez-Badillo, A. Islas-Jácome, M.A. Rentería-Gómez, S.G. Pharande, C.J. Cortes-García, M.A. Rincón-Guevara, I.A. Ibarra, R. Gámez-Montaño, E. González-Zamora. *Org. Biomol. Chem.* **2017**, *15*, 2363. (*Front cover of the issue*)

2 I.A. Ibarra, A. Islas-Jácome, E. González-Zamora. *Org. Biomol. Chem.* **2018**, *16*, 1402. (*Front cover of the issue*)

New route for the synthesis of 1,3,4-thiadiazine and 1,3,4-thiadiazole derivatives *via* multi-component reaction using thiocarbohydrazide

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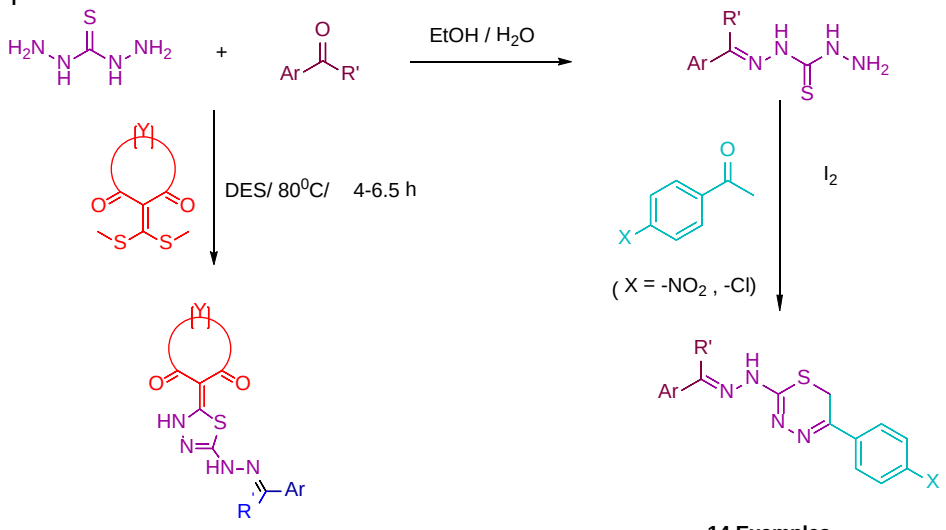
Among the wide range of an important structures of heterocycles, which containing sulfur and nitrogen atoms are in a special position due to their diverse applications especially due to their biological properties.[1-3] In the follow-up to our previous research on the synthesis of heterocycles,[4] here we report new route for the synthesis of novel derivatives of 1,3,4-thiadiazole and 1,3,4-thiadaizine.

At first, the reaction between thiocarbohydrazine, various carbonyl compounds, acetophenone derivatives and iodine will be discussed. This reaction leds to formation of new 1,3,4-thiadaizine derivatives which carried out under reflux and on metal-free catalyst condition (Scheme 1).

In the following, a one-pot, three-component synthesis of new substituted 1,3,4-thiadiazole derivatives using a ketene *S*,*S*-acetal, a carbonyl compound and thiocarbohydrazide (Scheme 1) in Deep Eutectic Solvent (DES) will be described. The main advantages of this reaction are high yields in suitable times, simple reaction conditions, green reaction medium and one-step synthesis manner. The structures of products were deduced from their spectroscopic data.



References:

1 (a) S. Fustero, M. Sánchez-Roselló, P. Barrio, A. Simón-Fuentes, *Chem. Rev.* **2011**, *111*, 6984; (b) V. Sridharan, P. A. Suryavanshi, J. C. Menéndez, *Chem. Rev.* **2011**, *111*, 7157.

2 A. R. Katritzky, Handbook of Heterocyclic Chemistry, (Pergamon Press, New York: **1985**).

3 S. V. Usol'tseva, G. P. Andronnikova, V. S. Mokrushi, *Chem. Heterocycl. Compd.*, **1991**, *27*, 343.

4 (a) A. Habibi, Y. Valizadeh, A. Alizadeh, *Helvetica Chimica Acta* **2015**, *98*, 67; (b) H. R. Qomi, A. Habibi, *Tetrahedron* **2017**, *73*, 2991.

Exploitation of the Cu-catalyzed A3 coupling for the Diversity Oriented Synthesis of proline-derived peptidomimetics

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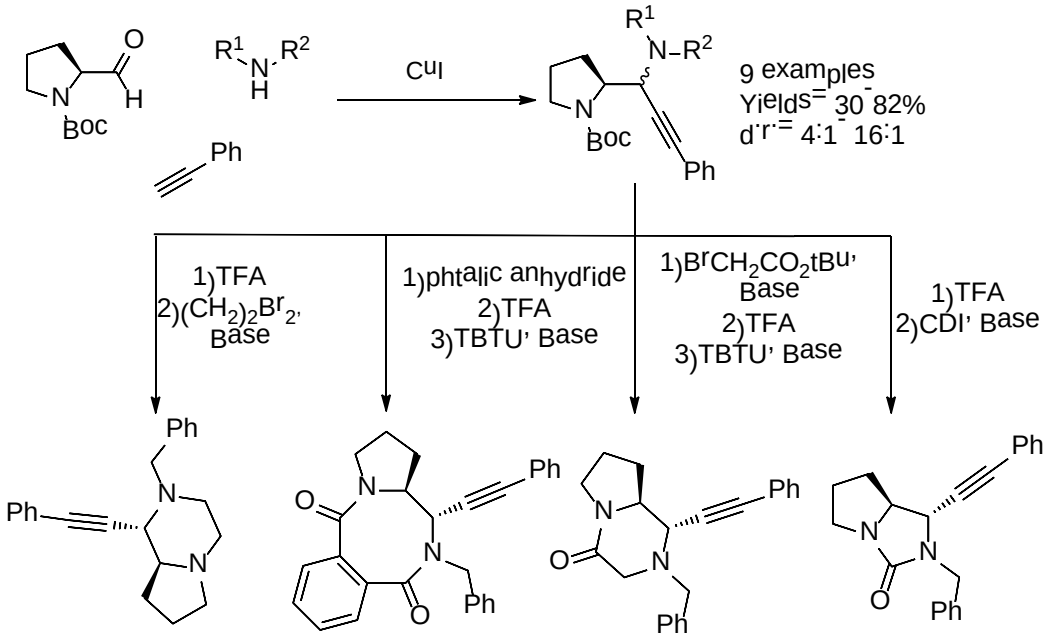
Diversity Oriented Synthesis (DOS)[1] has been placed as a new paradigm for the revival of drug discovery. DOS consists of generating structurally diverse compounds from simple starting materials, by exploiting economic synthetic strategies, such as the Build/Couple/Pair approach, composed of no more than five steps. In this approach, the Aldehyde-Amine-Alkyne reaction (A3)[2] proves to be an interesting methodology as a coupling step, because it can lead to the formation of poly functionalized intermediate suitable for the creation of different molecular entities. In our work we used the amino aldehyde[3] derived from proline and nine different amines, resulting in the generation of propargylamines in 30-82% yield and with good diastereoselectivity. These products were successively exploited to obtain a library of different bicyclic compounds using different chemo and regio-selective intramolecular cyclization reactions.



References:

1 A. Trabocchi, Diversity *Oriented Synthesis: Basics and Applications in Organic Synthesis, Drug Discovery, and Chemical Biology*, John Wiley & Sons, 1stEd**., 2013**
2 V. A. Peshkov, O. P. Pereshivko and E. V. Van der Eycken, *Chem. Soc. Rev*. **2012**, 41, 3790
3 D. Gryko, J. Chałko, and J. Jurczak, *Chirality*, **2003**, 15, 514

Gold Nanoparticles into the MCR Universe: One-Pot Synthesis of Dihydroquinoxalin-2-ones via the Chemoselective Transfer Hydrogenation of Multifunctional Nitro Derivatives

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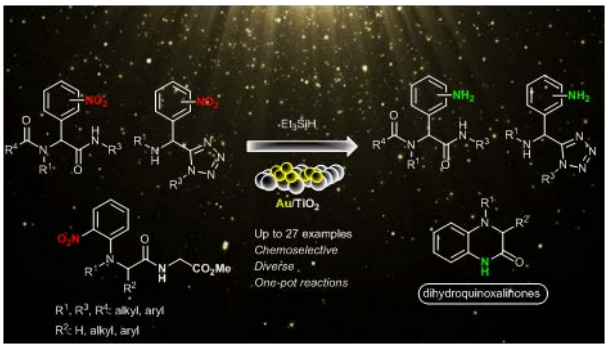
Multi-Component Reactions (MCRs) are very often tagged as atom economic, step efficient with high exploratory power with regard to chemical space, processes. It is an important method since carbon-carbon, carbon-nitrogen, carbon-oxygen and amide bonds are created in a single stage.[1,2] The facile titania-supported gold nanoparticles catalyzed chemoselective reduction of multifunctional nitro-compounds into the corresponding amines in high isolated yields, employing Et_3SiH as reducing agent,[3] is reported. Remarkably, the same transfer hydrogenation process was found to be efficient even for more complex molecules such as tetrazole or amino acid substituted derivatives.[4] The present catalytic system represents an expeditious approach towards the production of the heterocyclic dihydroquinoxalin-2-ones with high yields, via a two-step one-pot ring closing pathway based on the reported chemoselective reduction.[5]



References
[1] A. Domling, *Chem. Rev.* **2006**, 106, 17.
[2] A. Domling, I. Ugi, *Angew. Chem. Int. Ed.* **2000**, 39, 3168.
[3] a) S. Fountoulaki, V. Daikopoulou, P. L. Gkizis, I. Tamiolakis, G. S. Armatas, I. N. Lykakis, *ACS Catal.* **2014**, 4, 3504; b) Gkizis, P. L.; Stratakis, M.; Lykakis I. N. *Catal. Commun*. **2013**, 36, 48.
[4] D. Iordanidou, T. Zarganes-Tzitzikas, C. G. Neochoritis, A. Dömling, I. N. Lykakis, *J. Org. Chem*. **2018** *submitted*.
[5] The program of State Scholarships Foundation (IKY) for graduate studies is kindly acknowledged.

Synthesis of eight-membered azocinoquinolines through sequential Ugi-4CR/Palladium-catalyzed hydride capture reaction

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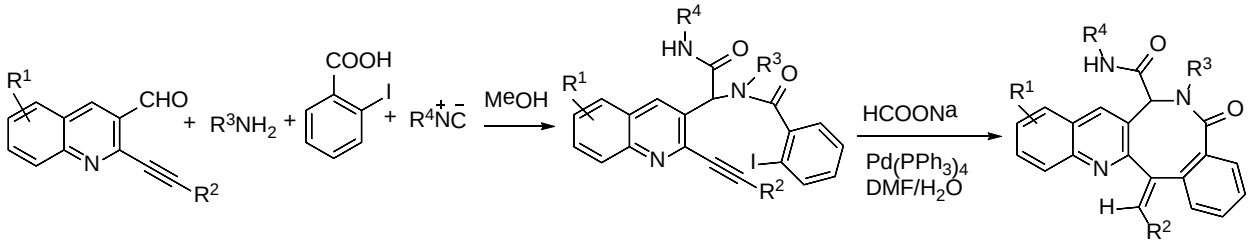
Synthesis of medium-sized heterocycles, which are a highly relevant motif in many bioactive natural products and pharmaceutical chemistry like Manzamine A, Keramine-A, Balasubramide and Arcyroxocin A, by palladium-catalyzed transformations have seen a fascinating development in recent years.[1] Similarly the utilization of alkynes in the intramolecular palladium-catalyzed synthesis of heterocycles represents one of the most versatile and efficient tools for the preparation of this class of compounds.[2]

As a part of our explorations toward the synthesis of natural products analogues, we have investigated an efficient rout for the synthesis of rare quinoline fussed nitrogen containing eight-membered 1,2-dihydroazocino[4,3-*b*]quinolin-3-one skeletons. The sequence starts with Ugi-4CR by means of preparing the appropriate substrate for further intramolecular Palladium-mediated reductive Mizoroki-Heck cyclization reaction.

The reaction is stereo- and regioselective, therefore the *trans* hydroarylated products are isolated in the 8-exo-dig mode of cyclization in short reaction time and high yields. Derivatives have been synthesized, characterized and will be discussed in poster presentation.



$R^{1=}$ Methyl, Ethyl, 2,3-Dimethyl
$R^{2=}$ Phenyl, Cyclopropyl, Pentylphenyl
$R^{3=}$ Benzyl, Ethylphenyl
$R^{4=}$ *tert*-Buthyl, Cyclohexyl

1. Van der Eycken E., Appukkuttan P., Sharma A., *Chem. Commun.,* **2012**, *48*, 1623-1637.
2. Yamamoto Y., *Chem, Soc. Rev*., **2014**, *43*, 1575.

Synthesis of Heterocyclic Ferrocene Derivatives by Multicomponent Reactions

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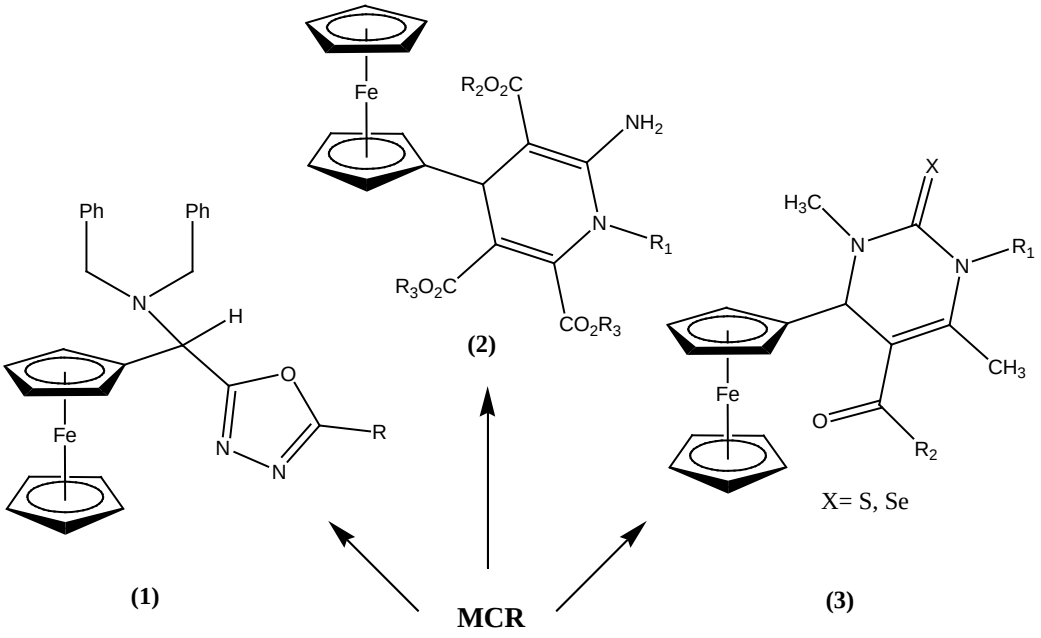
Ferrocene derivatives have numerous applications in the various area.[1] Nowadays many organic compounds can be synthesized by multicomponent reactions (MCRs).[2, 3] Various heterocycles can be prepared by MCRs.[4] In connection with our interest for the synthesis of heterocycles,[5] we report the synthesis of ferrocenyl containing 1,3,4-oxadiazole derivatives **(1)**, solid phase synthesis of ferrocenyl derivatives of 1,4-dihydropyridines **(2)**, and solid phase synthesis of 4-(ferrocenyl)-2-sulfanylidene-1,2,3,4-tetrahydropyrimidine or 4-ferrocenyl-1,2,3,4-tetrahydro-2-selenoxopyrimidine derivatives **(3) (Scheme 1)**.



Scheme 1. Synthesis of heterocyclic ferrocene derivatives by multicomponent reactions.

References:

1 Larik, F, A,; Saeed, A.; Fattah, T. A.; Muqadar, U.; Channar, P. A. *Appl. Organometal. Chem*. **2016**, *30*, 3664.
2 Dömling, A. *Chem. Rev*. **2006**, *106*, 17.
3 Shaabani, A.; Maleki, A.; Rezayan, A. H.; Sarvary, A. *Mol. Divers*. **2011**, *15*, 41.
4 Sadjadi, S.; Heravi, M. M.; Nazari, N. *RSC. Adv*. **2016**, *6*, 53203.
5 Kazemizadeh, A. R.; Hajaliakbari, N.; Hajian, R.; Shajari, N.; Ramazani, A. *Helv. Chim. Acta* **2012**, *95*, 594; b) Kazemizadeh, A. R.; Shajari, N.; Shapouri, R.; Adibpour, N.; Teimuri-Mofradd, R.; Dinmohammadi, P. *Appl. Organometal. Chem*. **2016**, *30*, 148.

Novel Modular One-Pot Synthesis of 3,7-Disubstituted Phenothiazine Based Donor Systems as Potential TADF Chromophores

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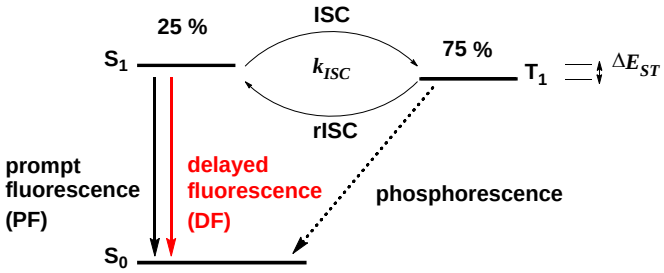
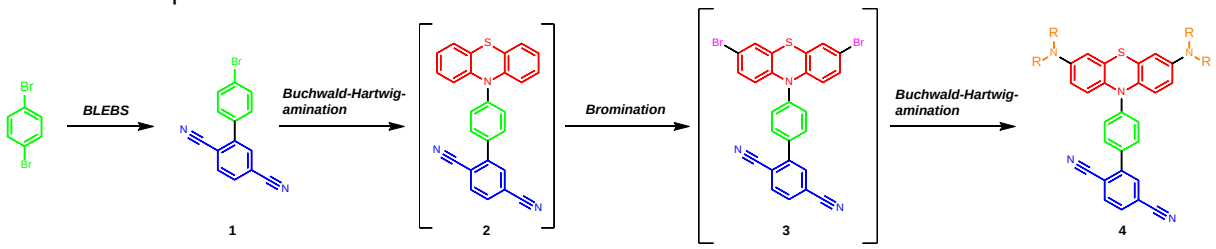
Lately organic molecules showing thermally activated delayed fluorescence (TADFs) have intensively been explored as potential emitters in organic light emitting diodes (OLEDs). As a consequence of their favorable photophysical properties they are expected to enable new OLED applications with broad flexibility at low costs.[1]



One strategy for designing TADF chromophores lies in the ligation of donor and acceptor parts that are separated by a phenyl unit. A powerful donor system, which just recently has been employed in TADF molecules, is phenothiazine.[2]

Here, we propose a novel modular one-pot synthesis of phenothiazine-acceptor conjugates. For this purpose, we created the acceptor linker molecules 1 by *BLEBS* (*Bromine-Lithium Exchange-Borylation-Suzuki-Coupling*) sequence in a one-pot fashion.[3] The first-generation TADF-system 2 is synthesized via *Buchwald-Hartwig* amination with *10H*-phenothiazine and the substituted aryl halides 1.[4] Subsequent bromination and *Buchwald-Hartwig* amination led to the targeted second-generation chromophores with enhanced donor strength 4 by introduction of electron-rich substituents at positions 3 and 7 of the phenothiazine unit.[3,5]



References:
[1] C. Adachi, *Jpn. J. Appl. P.,* 2014, *53*, 060101-1 - 060101-11.
[2] J. S. Ward, R. S. Nobuyasu, A. S. Batsanov, P. Data, A. P. Monkman, F. B. Dias, M. R. Bryce, *Chem. Commun.*, 2016, *52*, 2612-2615.
[3] A. W. Franz, T. J. J. Müller, *Synthesis,* 2008, *7*, 1121-1125.
[4] C. Dostert, C. Wanstrath, W. Frank, T. J. J. Müller, *Chem. Commun.*, 2012, *48*, 7271-7273.
[5] I. S. Pereteanu, T. J. J. Müller, *Org. Biomol. Chem.,* 2013, *11,* 5127-5135.

Genetic tagging of the Ugi-four-component reaction

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DNA-encoded libraries (DELs) have emerged as a validated screening technology for the identification of small bioactive molecules that perturb the activity of pharmacologically interesting targets. They consist of organic compounds covalently attached to individual DNA sequences carrying information about the molecule structure. Genetic tagging of small molecules allows for efficient synthesis and handling of large pooled compound libraries that can be screened on proteins by affinity-based selection assays. Enriched protein binders are identified from complex compound mixtures by DNA sequencing.
Multicomponent reactions (MCR) offer many advantages over sequential multistep synthesis such as atom economics, efficiency and convergence.[1,2] Moreover, a broad set of diverse molecular architectures can be generated in often straightforward manner from simple starting materials, thus MCR chemistry represents an excellent technology for the fast and efficient library synthesis. To establish the Ugi-four-component reaction (U-4CR) for DEL synthesis, we utilize our solid phase-bound hexathymidine “hexT” approach that tolerates a broad spectrum of reaction conditions, reagents and catalysts (Figure 1A).[3] hexT DNA functions also as an adapter oligonucleotide to which coding DNA sequences with a hexaadenosine overhang can be readily ligated (Figure 1B). Using optimized U-4CR reaction conditions on DNA an 8.000-membered DEL specifically targeting Mdm2 is under preparation.

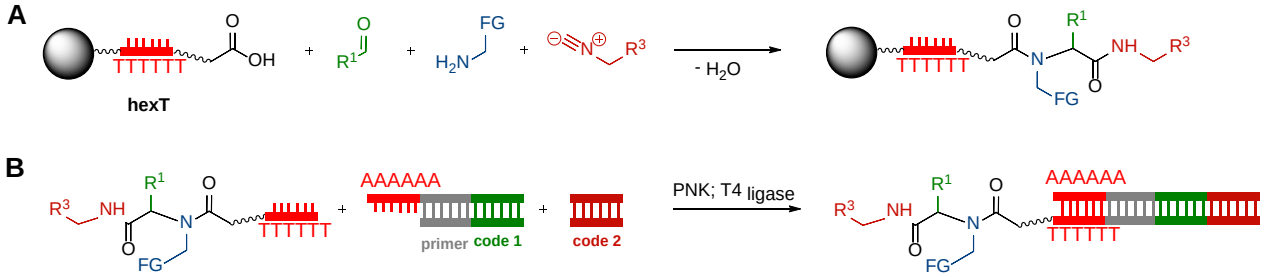

Figure 1: Ugi-four-component reaction in DEL synthesis (A) and coding strategy with our hexT approach (B). FG: functional group for combinatorial library expansion.

References:

1 A. Dömling, W. Wang, K. Wang, *Chem. Rev.* **2012**, *112*, 3083-3135.
2 A. Dömling, I. Ugi, *Angew. Chem. Int. Ed.* **2000**, *39*, 3168-3210.
3 M. Klika Škopić *et al.*, *Chem. Sci.* **2017**, *8*, 3356-3361.

Tyrosinases in Organic Synthesis – Mediating the α-arylation of β-dicarbonyl compounds

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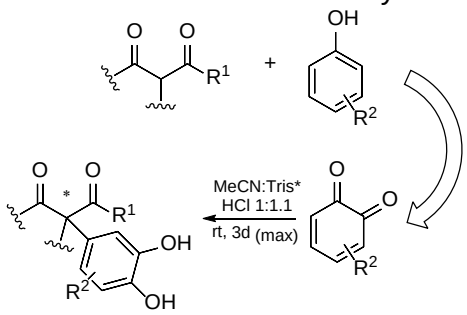
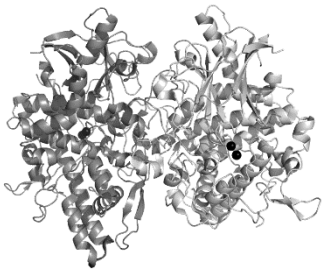
The interest in performing green/environmentally benign chemistry increased within the last decade, moving enzyme mediated reactions also into the focus of organic chemistry. Among them, oxidoreductase-mediated arylations aroused our interest. Tyrosinases, as members of the class of multi copper-oxidases, are widespread in all domains of life.[1] Their ability to not only exhibit a catecholase, but also a phenolase activity towards low-molecular weight compounds, turn the multicopper oxidases into beneficial and versatile alternatives compared with toxic and expensive oxidizing agents.[1,2] We present our recent findings in the field of copper-oxidase-mediated synthesis of building blocks for active agents. The tyrosinase from *Aspergillus oryzae*[3] could be established in our working group to investigate its application in organic synthesis. With respect to enzyme-mediated arylation reactions, the substrate scope of the given tyrosinase was investigated.[4] These results represent an update of the former published laccase mediated arylations.[5]





1 S. Witayakran, A. J. Ragauskas, *Adv. Synth. Catal*. **2009**, *351*, 1187-1209.
2 N. Fujieda, S. Yabuta, T. Ikeda, T. Oyama, N. Muraki, G. Kuriso, S. Itoh, *J. Bio. Chem*. **2013**, *288*, 22128-22140.
3 N. Fujieda, M. Murata, S. Yabuta, T. Ikeda, C. Shimokawa, Y. Nakamura, Y. Hata, S. Itoh, *ChemBioChem.* **2012**, *13*, 193-201.
4 R. Krug, D. Schröder, J. Gebauer, S. Suljić, N. Fujieda, Y. Morimoto, S. Itoh, J. Pietruszka, *Eur. J. Org.Chem*. **2018**, *2018*, 1789-1796.
5 a) J. Pietruszka, C. Wang, *Green Chem*. **2012**, *14*, 2402-2409; b) S. Suljić, F. B. Mortzfeld, M. Gunne, V. B. Urlacher, J. Pietruszka, *ChemCatChem*. **2015**, *7*, 1380-1385; c) S. Suljić, J. Pietruszka, *Adv.Synth.Catal*. **2014**, *356*, 1007-1020; d) J. Pietruszka, C. Wang, *ChemCatChem*. **2012**, *4*, 782-785.

Synthesis of Highly Substituted 1,3-oxazinan-2-one derivatives via Ugi Reaction

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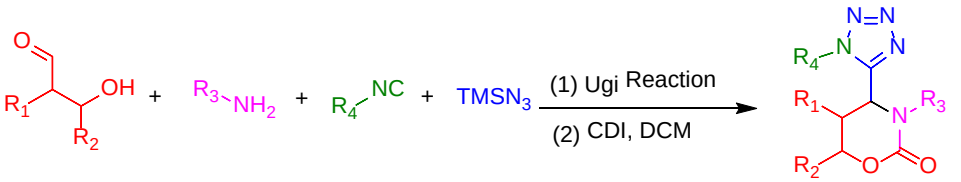
1,3-Oxazinan-2-one derivatives are very potent heterocyclic compounds with remarkable biochemical activities and widely used in drug discovery.[1] There are many synthetic routes to 1,3-oxazinan-2-ones. Most of them involve phosgene or its derivatives, alkyl halide chemistry and isocyanate compounds.[2] Other procedures require complex starting materials or multiple steps to give the final product.[3] However, these synthetic routes have several drawbacks such as harsh conditions, low yields due to multiple steps and limited substitution pattern and diversity. Herein, we introduce a 2 steps synthesis of 1,3-oxazinan-2-one derivatives which have at least 4 substitutions with high yields using multicomponent reaction chemistry. The large scale amenable building blocks can be further substituted at up to four positions, making this a very versatile scaffold synthesis strategy. Our methods thus fulfill the increasing demand for novel building block design and nontraditional scaffolds which previously were not accessible.



15 examples
up to 80% yield

References:

1 (a) G. Wang, J. R. Ella-Menye, et al., *Bioorg. Med. Chem. Lett*. **2006**, *16(8),* 2177-2181. (b) Z.. Xu, C. M. Tice, et al., J. *J. Med. Chem.*, **2011**, *54(17),* 6050-6062..

2 (a) F. Aricò, S. Bravo, et al., *Pure Appl. Chem*., **2016**, *88(3),* 227-237; (b) S. Trifunovic, D. Dimitrijevic, et al., *Synthesis* **2010**, *06*, 943-946; (c) I. Shibata, K. Nakamura, et al., *Chem. Soc. Jpn*., **1989**, *62*, 853

3 S. Mangelinckx, Y. Nural, et al., Tetrahedron. **2010**, *66*, 4115

Multicomponent synthesis and binding mode of imidazo[1,2- *a*]pyridine-capped selective HDAC6 inhibitors

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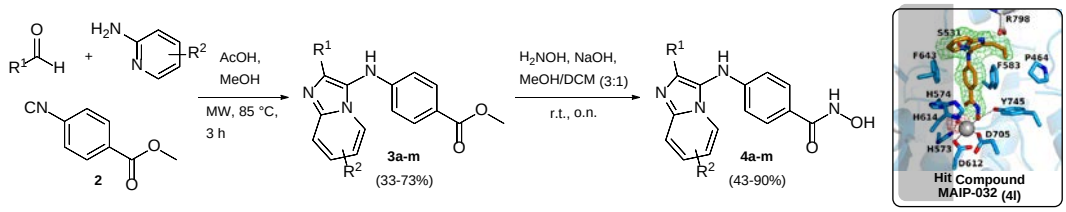
The class IIb isozyme histone deacetylase 6 (HDAC6) modulates the function of many non-histone proteins such as α-tubulin and Hsp90, and it participates in numerous diseases.[1] For instance, HDAC6 shows high expressions in several cancer types and has therefore been identified as a promising drug target.[1,2] Recently, it has been reported that HDAC6 differs distinctly in its structural features compared to other HDAC isoforms, which can be utilized for the design of selective HDAC6i.[2] Herein, we report on the design, diversity-oriented synthesis, and biological evaluation of novel imidazo[1,2-*a*]pyridine-based hydroxamic acids as selective HDAC6 inhibitors.

To synthesize the target compounds, we optimized and applied the highly versatile *Groebke-Blackburn-Bienaymé* three-component (GBB-3CR, **3a-m**) reaction as the key step, resulting in a microwave assisted synthetic protocol with yields ranging from 33-73 %. The required isocyanide **2** for the GBB-3CR was synthesized in a straightforward two-step synthesis starting from methyl 4-aminobenzoate with 93 % overall yield. The final step of the synthesis included the aqueous hydroxylaminolysis to yield the desired hydroxamic acids in 43-90 % yield (**4a-m**).

The biological evaluation of this mini-library led to the discovery of the hit compound MAIP-032 (**4l**, IC_{50} (HDAC6) = 0.058 µM) as a selective HDAC6 inhibitor (SI: HDAC1 = 38; HDAC2 = >172; HDAC3 = >172; HDAC8 = 27). Western blotting experiments amplified these findings, as compound MAIP-032 only induced the acetylation of α-tubulin, but not of histone H3. Furthermore, MAIP-032 displayed promising anticancer activity (IC_{50} (Cal27) = 3.87 µM) and flow cytometric analysis showed that its cytotoxic effect was mediated by apoptosis induction even in a low concentration of 1 µM. In addition, the X-ray structure of catalytic domain 2 from *Danio rerio* HDAC6 complexed with our HDAC6i MAIP-032 revealed a unique monodentate zinc-binding mode, thus giving structural insights that can be exploited further in the design of HDAC6-selective inhibitors. Taken together, these results suggest that MAIP-032 is a promising candidate for further optimization as selective HDAC6i.



One-pot Synthesis of Donor-Acceptor Conjugates and their Solar Cell Application

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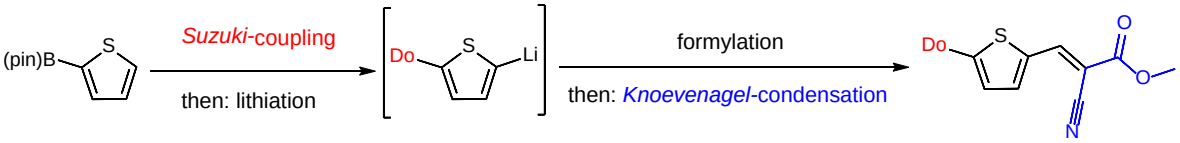
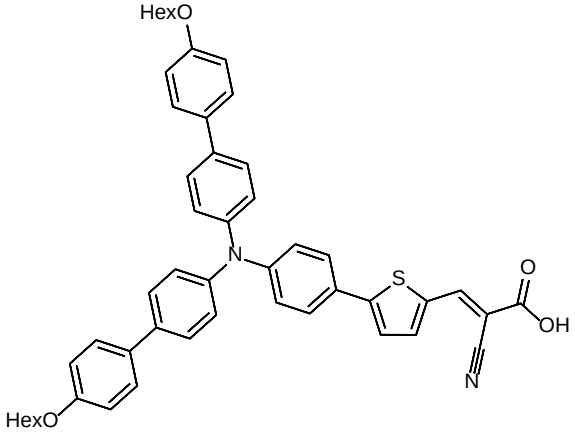
Functional chromophores as sensitizers for organic metal-free dye sensitized solar cells (DSSC) have been employed in solar cell devices with respect to the development of both more sustainable and efficient solar-cell technologies.[1,2] Small structural changes of the sensitizers can affect the overall efficiency of the solar cell devices quite strongly. Therefore, the synthesis of highly diverse substance libraries is desirable to gain a deeper insight into structure-property relationships and to further optimize the sensitizers.[3,4,5]
Here, we propose a novel, versatile and efficient one-pot synthesis based on a *Suzuki*-coupling-formylation-*Knoevenagel*-condensation sequence, which is a powerful tool for the rapid synthesis of various thiophene-donor-acceptor conjugates starting from simple molecules.



Do = donor **donor-acceptor conjugates**

With this method in hand we synthesized several potential DSSC dyes with high yields. Photophysical and electrochemical data of selected dyes were examined. Ultimately, triphenylamine dye **1** showed a high overall efficiency in solar cell experiments.



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References:

1 B. Pashaei, H. Shahroosvand, M. Graetzel, M. K. Nazeeruddin, *Chem. Rev.* **2016**, *116*, 9485-9564.
2 T. Meyer, D. Ogermann, A. Pankrath, K. Kleinermanns, T. J. J. Müller, *J. Org. Chem.* **2012**, *77*, 3704.
3 S. Fuse, S. Sugiyama, M. M. Maitani,Y. Wada, Y. Ogomi, S. Hayase, R. Katoh, T. Kaiho, T. Takahashi, *Chem. Eur. J.* **2014**, *20*, 10685 – 10694.
4 T. Meyer, *Dissertation* **2014**, HHU Düsseldorf.
5 A. Mishra, M. K. R. Mishra, P. Bäuerle, *Angew. Chem. Int. Ed.* **2009**, *48*, 2474-2499.

Diversity-oriented Three-component Synthesis of 3,10-Diaryl Phenothiazines *via* Sequential Palladium Catalysis

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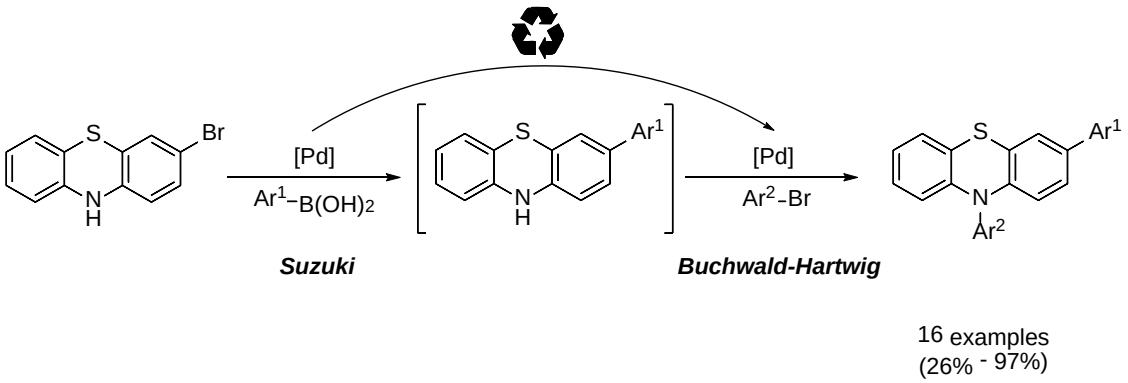
Phenothiazines, important tricyclic nitrogen-sulfur heterocycles, possess low, reversible first oxidation potentials with a pronounced propensity to form stable radical cations. As a consequence, these favorable electronic properties of phenothiazines have led to applications as multi-functional emitting materials in organic light emitting diodes[1], as hole-transporting materials for high-performing Perovskite solar cells[2] and as visible light photoredox catalysts[3].
Sequentially Pd-catalyzed processes based upon cross-coupling reactions are excellent entries to heterocycle synthesis.[4] Here, we report a sequentially Pd-catalyzed synthesis of 3,10-diaryl phenothiazines employing *Suzuki* coupling and *Buchwald-Hartwig* amination in a one-pot fashion.



Optical spectroscopy reveals considerable fluorescence with emission of blue to yellow and large Stokes shifts for all systems. Cyclic voltammetry shows a distinct *Nernstian*-reversible redox behavior for the first one-electron oxidations. Their potential strongly depends on the electronic nature of the substituent of the benzo ring. In a consanguineous series of *para*-substituted 3,10-diaryl phenothiazines a three-dimensional LFER can be established by correlation of first oxidation potentials and the corresponding *Hammett* substituent parameters.

[1] M. Okazaki, Y. Takeda, P. Data, P. Pander, H. Higginbotham, A. P. Monkman, S. Minakata, *Chem. Sci.* **2017**, *8*, 2677-2686.
[2] R. Grisorio, B. Roose, S. Colella, A. Listorti, G. P. Suranna, A. Abate, *ACS Energy Lett.* **2017**, *2*, 1029-1034.
[3] a) H. Wang, N. T. Jui, *J. Am. Chem. Soc.* **2017**; b) S. Dadashi-Silab, X. Pan, K. Matyjaszewski, *Chem. Eur. J.* **2017**, *23*, 5972-5977.
[4] T. Lessing, T. J. J. Müller, *Appl. Sci.* **2015**, *5*, 1803-1836.

Nonconjugated donor-acceptor-systems for intramolecular photoinduced electron transfer

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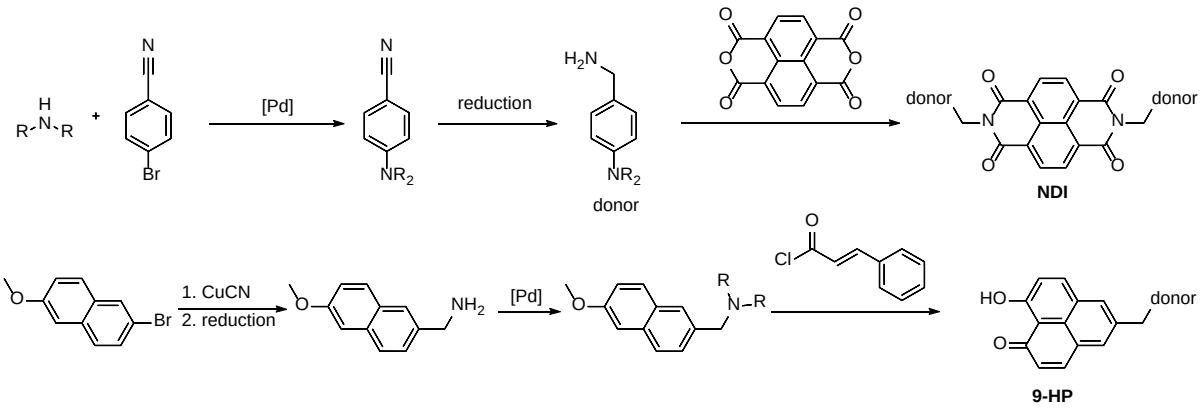
Donor-acceptor-systems with a lack of conjugation between the donor and acceptor have the potential to stabilize their excited state by an intramolecular electron transfer[1,2] leading to charge separated diradical ion pairs and, thus, to an increased magnetic moment[3]. When adsorbed on a metallic surface these compounds could serve as optically addressable switches in a binary manner in logical devices on a molecular scale.
In this project naphthalenediimide (NDI) and 9-hydroxyphenalenone (9-HP) are employed as planar acceptors linked to nitrogen-containing donors like carbazole or dimethylpyrrole. The donor-acceptor-systems are synthesized from easily accesible starting materials *via* Pd-catalyzed *Buchwald-Hartwig* aminations, reduction of aromatic nitriles, and employing microwave assisted synthesis.



Scheme 1: Methylene-linked donor-acceptor-systems for the intramolecular electoron transfer.

[1] G. J. Kavarnos in *Fundamentals of Photoinduced Electron Transfer*, Wiley VCH Verlag GmbH, New York, **1993**.
[2] J. R. Lakowicz, in *Principles of Fluorescence Spectroscopy* (Ed.: J. R. Lakowicz), Springer US, Boston, MA, **2006**.
[3] K. V. Raman, A. M. Kamerbeek, A. Mukherjee, N. Atodiresei, T. K. Sen, P. Lazić, V. Caciuc, R. Michel, D. Stalke, S. K. Mandal, S. Bügel, M. Münzenberg, J. S. Moodera, *Nature,* **493**, 509-513.

DIVERSITY-ORIENTED SYNTHESIS OF QUINOXALINE BASED LUMINOPHORES: PHOTOPHYSICAL AND ELECTROCHEMICAL PROPERTIES

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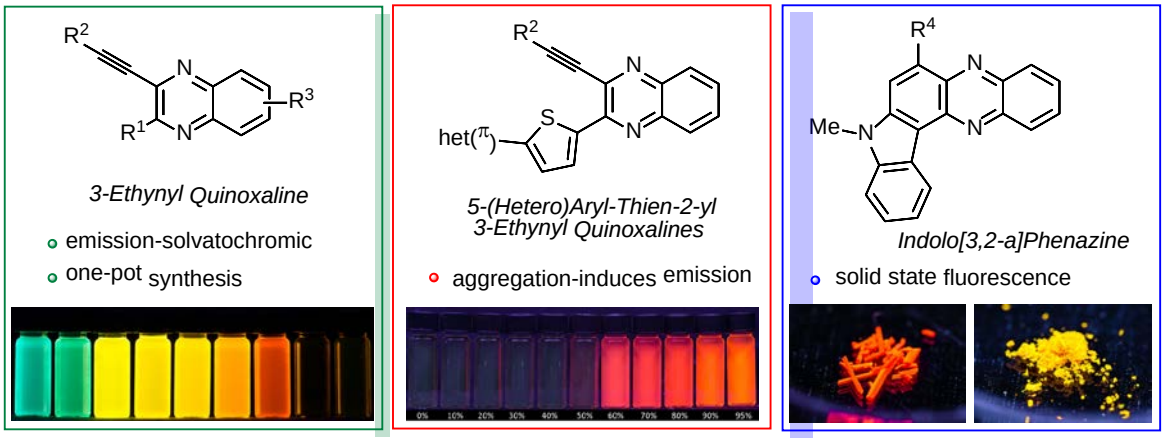
In the past decades, functional organic heterocyclic compounds have increasingly received interest in the context of materials and life sciences.[1] Especially fluorophores with designed emission characteristics have become growingly important[2] in the area of organic electronics and sensing applications. Fluorophores with colour response to the surrounding media are particularly interesting. Despite a facile preparation of those compounds is still one of the most challenging goals for a synthetic chemist. Our group has reported different syntheses using reactive ynediones[3] as in situ generated building blocks for the formation of functionalized heterocyclic molecular architectures. Based on this conceptual approach we further developed a set of complementary one-pot syntheses of fluorescent and solvatochromic 3-ethynyl quinoxalines[4], related 3-aminovinyl quinoxalines[5] and 5-(hetero)aryl-thien-2-yl substituted 3-ethynyl quinoxalines with aggregation induced emission characteristics.[6]



[1] Müller, T. J. J; Bunz, U. H. F, (eds.), *Functional Organic Materials*; WileyVHC, Weinheim, **2007**.
[2] Levi, L.; Müller, T. J. J.; *Chem. Soc. Rev.* **2016**, *45*, 2825–2846.
[3] Boersch, C.; Merkul, E.; Müller, T. J. J.; *Angew. Chem. Int. Ed.* **2011**, *50*, 10448–10452.
[4] (a) Gers, C. F.; Nordmann, J.; Kumru, C.; Frank, W.; Müller, T. J. J.; *J. Org. Chem.* **2014**, *79*, 3296-3310. (b) Merkt, F. K.; Höwedes, S. P.; Gers-Panther, C. F.; Gruber, I.; Janiak, C.; Müller, T. J. J., *Chem. Eur. J.* **2018**, *24*, DOI: 10.1002/chem.201800079.
[5] (a) Gers-Panther, C. F.; Fischer, H.; Nordmann, J.; Behnke, T.; Seiler, T.; Würth, C.; Frank, W.; Resch-Genger, U.; Müller, T. J. J.; *J. Org. Chem.* **2017**, *82*, 567-578. (b) Nirmalananthan, N.; Behnke, T.; Hoffmann, K.; Kage, D.; Gers-Panther, C. F.; Frank, W.; Müller, T. J. J.; Resch-Genger, U., *J. Phys. Chem. C*, **2018**, DOI: 10.1021/acs.jpcc.8b01425, *just accepted*.
[6] Merkt, F. K.; Müller, T. J. J.; *Sci. China Chem.* **2018**, *manuscript submitted*.

The Chemical Space of Multicomponent Reactions: A superior tool to explore novel, advanced materials

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Humanity needs a universal access to affordable, reliable, sustainable and modern energy for all. Novel, advanced materials is the key to this direction. Multi-Component Reactions (MCRs) is the process that enables building complex products in a single operation from three or more reactant starting molecules, which are very often tagged as atom economic, step efficient with high exploratory power regarding chemical space.[1,2] The rapid and easy access to biologically or material-relevant compounds by MCRs and their scaffold diversity (more than 700 different scaffolds) have been recognized by the synthetic community both in industry and academia as a preferred method to design and discover compounds with an increasing number of applications.[3] We wish to present our very recent advances in MCR concerning the synthesis of libraries of compounds relevant to organic (super)conductors, photovoltaics and optics.

Tetrathiafulvalene (TTF), one of the most important and well-studied electron donors,[4] has provided many organic metals and superconductors[5] and, more recently, multifunctional materials combining conductivity and magnetism, conductivity and chirality.[6] Functionalization of TTF still remains a hot topic;[7] we were able to synthesize in high yields several, novel covalent donor-acceptor systems consisting of TTF and various heterocycles (figure 1). We successfully functionalized the TTF and constructed flat, aromatic systems with strong electron withdrawing groups (EWG) as were dictated by thorough *ab initio* calculations. These systems have further been studied electrochemically (differential pulse voltammetry, UV-VIS spectra etc). Similar to TTF, more moieties that proved to have superconductivity properties e.g. *p*-terphenyl and phenathrene-type molecules,[8] have very easy been functionalized and subsequently been assembled in MCR scaffolds.

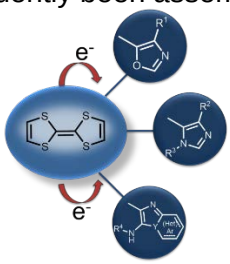

Figure 1. Assembly of TTF with electron withdrawing heterocycles utilizing the MCR platform

References:

[1] A. Dömling, W. Wang, K. Wang, *Chem. Rev.* **2012**, *112*, 3083–3135.
[2] A. Dömling, *Chem. Rev.* **2006**, *106*, 17–89.
[3] P. Slobbe, E. Ruijter, R. V. A. Orru, *Medchemcomm* **2012**, *3*, 1189.
[4] N. Martín, *Chem. Commun.* **2013**, *49*, 7025.
[5] X. Sun, G. Lai, Z. Li, Y. Ma, X. Yuan, Y. Shen, C. Wang, *Beilstein J. Org. Chem.* **2015**, *11*, 2343–2349.
[6] F. Pop, N. Avarvari, *Chem. Commun.* **2016**, *52*, 7906–7927.
[7] J. Nafe, F. Auras, K. Karaghiosoff, T. Bein, P. Knochel, *Org. Lett.* **2015**, *17*, 5356–5359.
[8] X. F. Wang, R. H. Liu, Z. Gui, Y. L. Xie, Y. J. Yan, J. J. Ying, X. G. Luo, X. H. Chen, *Nat. Commun.* **2011**, *2*, 507.

β-Amino Enoates and Hydroxypyrazoles by highly efficient One-Pot Synthesis

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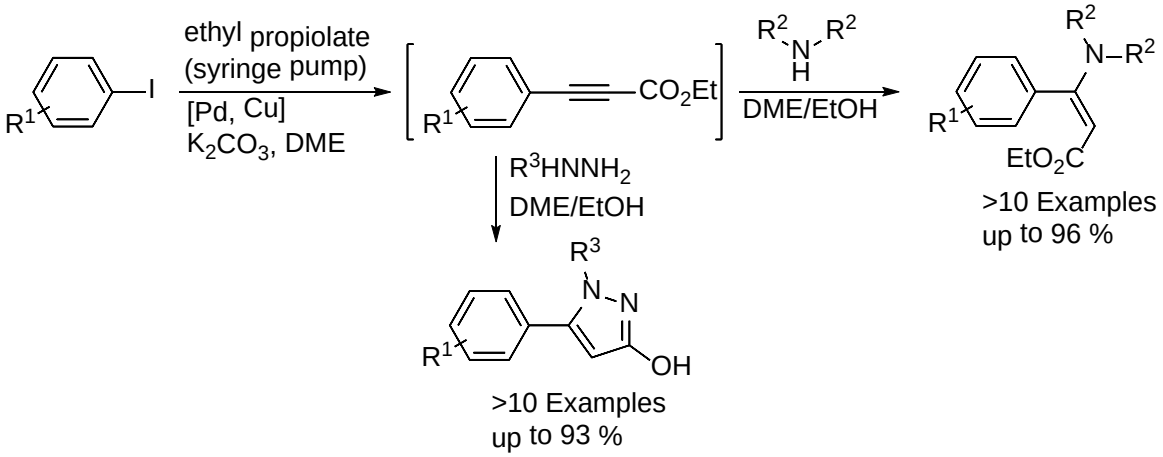
In heterocyclic synthesis, ethyl arylpropiolates are especially valuable because as Michael systems or dienophiles they can be excellently transformed into more complex structures.[1] Thus, a simple approach from aryl iodides covers a broad substituent spectrum in very good yields.[2] Substituted hydroxypyrazoles are particularly important constituents of biologically active synthetic building blocks and their synthesis receives great interest.[3] Starting from β-amino acrylates in the total synthesis of natural products, for example, β-amidoacrylates can be obtained.[4]

The aim of the work is the easy accessibility of hydroxypyrazoles and β-amino enoates in a sequential one-pot synthesis, i.e. without the isolation of ethyl arylpropiolate intermediates. Therefore, aryl iodides are coupled via Pd(0)/Cu(I)-catalized Sonogashira reaction with ethyl propiolate. Noteworthily, ethyl propiolate is added by syringe pump to circumvent unproductive side reactions. In the second step, biologically interesting hydroxypyrazoles are obtained using alkyl hydrazines via Michael addition and subsequent cyclocondensation in excellent yields. When employing secondary amines, a variety of β-amino acrylates can be obtained in excellent yields. Further transformation of the intermediate ethyl propiolate into heterocycles are currently underway.



Scheme 1: Consecutive three-component syntheses of hydroxypyrazoles and β-amino enoates via ethyl arylpropiolates.

References:

1 E. Schreiner, S. Braun, C. Kwasnitschka, W. Frank, T.J.J. Müller, *Adv. Synth. Catal.* **2014**, *356*, 14-15.
2 A.C. Götzinger, C.S. Michaelis, T.J.J. Müller, *Dyes Pigm.* **2017**, *143*, 308-316.
3 S. Bourrain, M. Ridgill, I. Collins, *Synlett.* **2004**, 795-798.
4 G. Zhu, Z. Chen, X. Zhang, *J. Org. Chem.* **1999**, *64*, 6907-6910.

Synthesis and Transformation of 1,2-Diketones *via* Sequentially Pd-Cu Catalyzed Multicomponent Reactions

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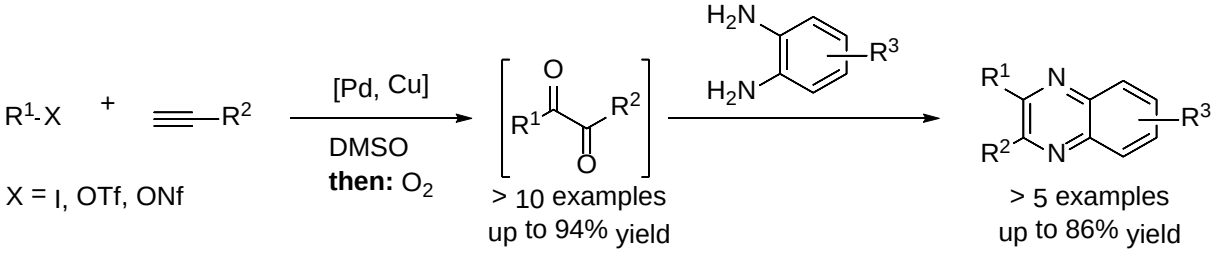
1,2-Diketones are very important structural units in biologically active molecules[1] that can be transformed into complex structures in organic synthesis.[2] A number of methods for the synthesis of 1,2-diketones have been developed where the Pd(II)- and Cu(II)-catalyzed oxidation of alkynes is considered to be one of the most practical strategies.[3]

The aim of the present work is the preparation of the 1,2-diketone moiety *via* a consecutive *pseudo*-four-component reaction while a single catalyst system is reused, without isolation of the intermediate alkyne. The sequence starts with a Pd(0)/Cu(I)-catalyzed *Sonogashira* coupling of a terminal alkyne and an aryl (pseudo)halide in DMSO. Subsequently, the solvent serves as an oxidant, whereas the catalyst system is reoxidized by molecular oxygen furnishing the desired product. Due to its modular nature the reaction sequence offers quick access to a broad range of variably substituted 1,2-diketones by virtue of the terminal alkyne and aryl (pseudo)halide. Electron releasing as well as withdrawing substituents are equally well tolerated.

1,2-Diketones can be transformed into quinoxalines, which are of interest as an important class of stable fluorescent heterocycles, finding use in several practical applications, such as laser dyes, emitters in light-emitting diodes, and as fluorescent sensors.[4] Based upon this strategy, we also report a one-pot synthesis of quinoxalines in a consecutive *pseudo*-five-component process. This sequence additionally includes a cyclocondensation transforming the 1,2-diketone to the corresponding heterocyclic compound (

Scheme **2**).

Moreover, different binucleophiles can also be employed in the one-pot sequence furnishing other heterocyclic systems. These processes are currently under investigation.



Scheme 2: Multi-component one-pot procedures for the synthesis of 1,2-diketones or quinoxalines.

[1] Maurya, R.; Singh, R.; Deepak, M.; Handa, S.S.; Yadav, P.P.; Mishra, P.K., *Phytochemistry* **2004**, *65*, 915-920.
[2] Deng, X.; Mani, N., *Org. Lett.* **2006**, *8*, 269-272.
[3] Gao, A.; Yang, F.; Wu, Y., *Tetrahedron* **2012**, *68*, 4950-4954.
[4] Aldakov, D; Palacios, M.A.; Anzenbacher, P., *Chem. Mater.* **2005**, *17*, 5238-5241.

Indium-catalyzed intramolecular 6-endo-dig cyclization for the synthesis of 3-(2-oxo-3,4-dihydro-2H-pyran-4-yl)-4H-chromen-4-ones

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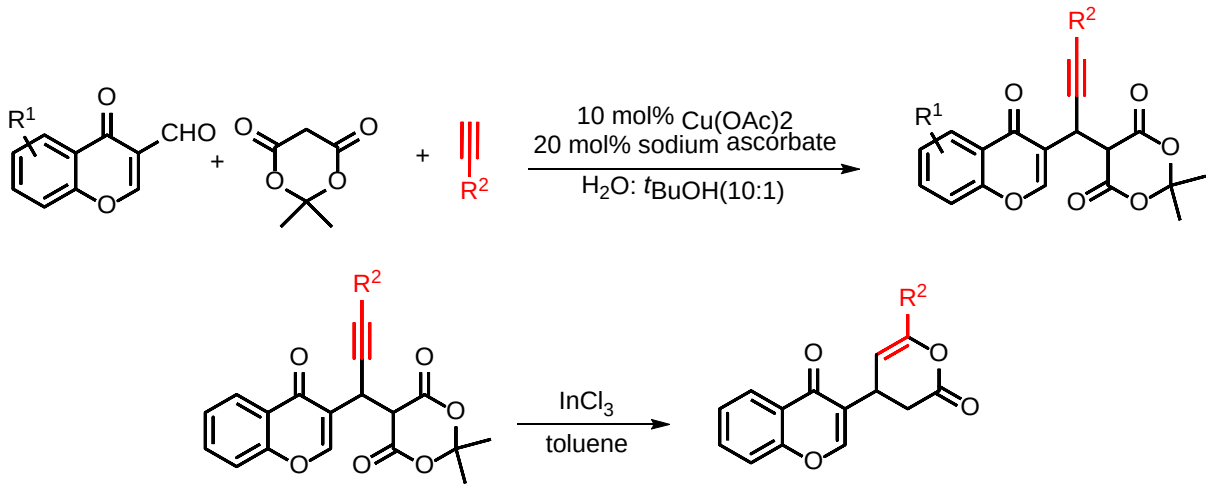
H-chromen-4-one and 3,4-dihydro-2H-pyran-2-one are important heterocyclic scaffolds with extended biological activities. Hence, there are considerable efforts toward the development of new approaches for the synthesis of these skeletons. In this regard, we report an efficient three-component reaction for the synthesis of an active compound-containing chromone, alkyne and Meldrum's acid (I). Furthermore, indium catalyzed intramolecular 6-endo-dig cyclization reaction is reported with the ultimate aim of synthesis of 3-(2-oxo-3,4-dihydro-2H-pyran-4-yl)-4H-chromen-4-ones. The structure of the products was confirmed based on spectroscopic data.



References:

1 T. F. Knöpfel, and E. M. Carreira, *J. Am. Chem. Soc.*, **2003**, 125, 6054–6055.
2 S. Li, W. Jia, N. Jiao, *Adv. Synth. Catal.* **2009**, 351, 569- 575.
3 A. M. Dumas, E. Fillion, *Acc Chem Res*, **2010**, 43, 440-454.

DABCO catalyzed MCR reactions: Synthesis of *trans,trans*-α,β,γ-substituted lactones

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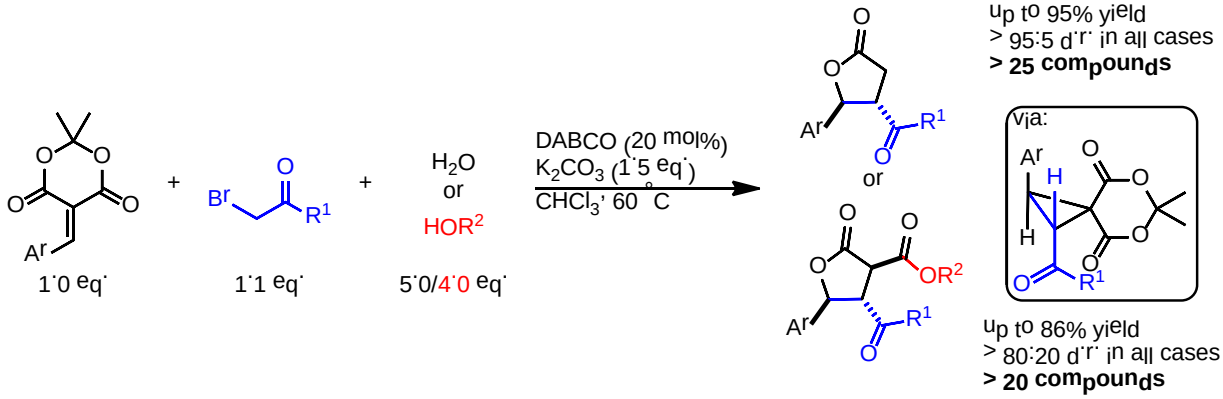
Nowadays, the use of ylides plays an important role in organic synthesis. While phosphorus and sulfur ylides have been exploited extensively in the past,[1,2] ammonium ylides have attracted considerably less attention. Based on this methodology a number of three membered and five membered ring systems have been synthesized. It has been shown, that cinchona alkaloids are suitable catalysts or reagents to perform enantioselective reactions.[3]

Our research focuses on the development of novel one pot reactions to access highly substituted compounds via ammonium ylides, employing cheap, commercially available starting materials. One example is the formation of *trans,(trans)*-α,β,(γ)-substituted lactones from phenacyl bromide, benzylidene meldrum's acid derivatives, and alcohols. γ-butyrolactones constitute an important structural motif which is found in many natural products[4-7] with interesting biological activities.[8,9]

The reactions proceeds via ammonium salt and ylide formation, 1,4-addition, cyclization to cyclopropanes, and rearrangement, generating the products in up to 95% yield with good to excellent diastereoselectivity.



References:

1 A.-H. Li, L.-X. Dai, V. K. Aggarwal, *Chem. Rev.* **1997**, *97*, 2341-2372.
2 E. M. McGarrigle, E. L. Myers, O. Illa, M. A. Shaw, S. L. Riches, V. K. Aggarwal, *Chem. Rev.* **2007**, *107*, 5841-5883.
3 D. Worgull, L. Öhler, J. P. Strache, T. Friedrichs, P. Ullrich, *Eur. J. Org. Chem.* **2017**, 6077-6080.
4 H. M. R. Hoffmann, J. Rabe, *Angew. Chem. Int. Ed.* **1985**, *24*, 94-110.
5 P. A. Grieco, *Synthesis* **1975**, 67-82.
6 W. Parker, J. S. Roberts, R. Ramage, *Quart. Rev. Chem. Soc.* **1967**, *21*, 331-363.
7 F. Schleth, T. Vogler, K. Harms, A. Studer, *Chem. Eur. J.* **2004**, *10*, 4171-4185.
8 K.-H. Lee, E.-S. Huang, C. Piantadosi, J. S. Pagano, T. A. Geissman, *Cancer Res.* **1971**, *31*, 1649-1654.
9 B. Mao, M. Fañanás-Mastral, B. L. Feringa, *Chem. Rev.* **2017**, *117*, 10502-10566.

Isocyanide Chemistry (IMCR): Promising Technology For Future Drug Discovery And Development

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In the last 5 years, the European Lead Factory (ELF) has successfully synthesized more than 500,000 new NCE's. Our laboratory is one of the research partners of the ELF that aims to develop new scaffolds for the synthesis of new libraries. Our main focus is on the isocyanide based multicomponent reactions (IMCR).

Isocyanides are stable organic compounds with a divalent carbon atom, which reacts with both - electrophiles and nucleophiles to give the α-addition products. If these electrophiles or nucleophiles come from two different chemicals, then it results in very interesting scaffolds, which might have been impossible to synthesize by the known traditional methods.[1] Combined with post-modifications, IMCR chemistry can afford elaborate and novel scaffolds with high diversity. The scaffold obtained from IMCR chemistry has more than three points of diversity. This helps us to synthesize innovative libraries with drug-like properties. Our lab submitted in total 61 novel scaffold proposals containing various macrocycles with more than one peptidomimetic bond and heterocyclic scaffolds to the ELF, out of which 55 proposals use IMCR chemistry.[2]

Furthermore, an analysis shows that more than 5% of the currently marketed drugs and their intermediates can be synthesized by IMCR in just a few steps, potentially lowering the production costs of medicines. Drugs synthesized by IMCR include lidocaine, Praziquantel (PZQ or Biltricide®), Carfentanil (Wildnil®), Lacosamide, Clopidogrel (Plavix®), Xylocaine, Almorexant, Telaprevir (Incivek®), Boceprevir (Victrelis®), Olanzapine (Zyprexa®), to name but a few.[3] To conclude, the advantages offered by isocyanides based multicomponent reactions (IMCR) make them a good alternative to conventional syntheses.

1. a) Doemling, A., *Chem. Rev*., **2006,** *106*, 17–89; b) El Kaim, L.; Grimaud, L.; Patil, P. *Org. Lett*. **2011**, *13*, 1261-1263.
2. a) Patil, P.; Khoury, K.; Herdtweck, E.; Doemling, A. *Org. Lett*. **2014,** *16*, 5736-5739; b) Patil, P.; Khoury, K.; Herdtweck, E.; Doemling, A. *Bioorg. Med. Chem.* **2015***, 23*, 2699-2715; c) Patil, P.; Madhavachary, R.; Kurpiewska, K.; Kalinowska-Tluscik, J.; Doemling, A. *Org. Lett.* **2017***, 19*, 642-645; d) Patil, P.; Mishra, B.; Sheombarsing, G.; Kurpiewska, K.; Kalinowska-Tluscik, J.; Doemling, A. *ACS Comb. Sci.* **2018***, 20*, 70-74, e) Abdelraheem, E. M. M.; de Haan, M. P.; Patil, P.; Kurpiewska, K.; Kalinowska-Tluscik, J.; Shaabani, S.; Doemling, A*. Org. Lett***.** **2017***, 19*, 5078-5081, f) Madhavacharya, R.; Abdelraheem, E. M. M.; Rossetti, A.; Twarda-Clapac, A.; Musielak, B.; Kurpiewska, K.; Kalinowska-Tłuścik, J.; Holak, T. A.; Dömling, A. *Angew. Chem., Int. Ed*. **2017**, *56*, 10725-10729; g) Liao, G. P.; Abdelraheem, E. M. M.; Neochoritis, C. G.; Kurpiewska, K.; Kalinowska- Tłuścik, J.; McGowan, D. C.; Dömling, A. *Org. Lett.* **2015***, 17*, 4980−4983; h) Abdelraheem, E. M. M.; Kurpiewska, K.; Kalinowska-Tłuścik, J.; Dömling, A. *J. Org. Chem*. **2016**, *81*, 8789−8795.
3. a) Ugi, I., Steinbrückner, C. (1959). DE-B1, 103, 337; b) Cao, H. P., Dömling, A. *Chem. A Eur. J*., **2010** 16, 12296-12298. c) Liu, H., William, S., Herdtweck, E., Botros, S., Dömling, A. *Chem. Biol. Drug. Des*., **2012**, 79, 470-477; d) Aissaoui, H., Cappi, M., Clozel, M., Fischli, W., Koberstein, R. (2001). PCT Int. Appl, *WO2001068609A120010920;* f) Znabet, A., Polak, M. M., Janssen, E., de Kanter, F. J. J., Turner, N. J., Orru, R. V. A., Ruijter, E. *Chem. Comm.,* **2010**, *46,* 7918-7920*;* g) Sollis, S. L. *J. Org. Chem.* **2005***, 70,* 4735-4740*.*

Multicomponent Synthesis of Bio-based Bicyclic Heterocycles from Levulinic Acid

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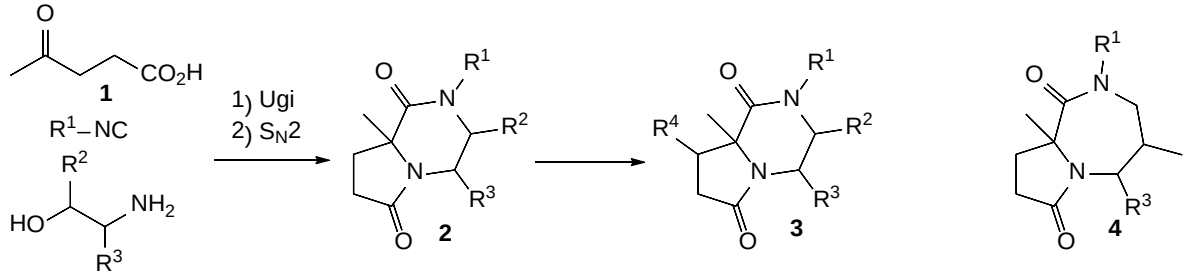
Levulinic acid **1** can be obtained from lignocellulosic materials of from waste sugar sources, being the product of acid catalysed degradation of hexoses. It is considered one of the most important biomass derived fine chemicals, and has already been extensively exploited in the polymer field.[1] We are curently interested in the diversity-oriented conversion of **1** into more complex, high added-value, heterocycles to be applied in the pharmaceutical field. Examples of isocyanide-based MCRs (IMCRs) starting from **1** have been already reported in the literature.[2] Capitalizing on our previous experience on IMCRs followed by S_N2 cyclizations,[3] we have now developed a short (2 steps) and operationally simple protocol for the high yield conversion of **1** and various biobased aminoalcohols into bicyclic heterocycles such as **2** and **4**. They incorporate classical "privileged structures", such as the pyroglutamic acid, the ketopiperazine and the diazepanone. Further diversity inputs have been introduced into compounds **2** and **4** by enolate alkylation. Starting from chiral enantiopure aminoalcohols, enantiopure **2**-**4** could be obtained.



References:

1 Hartweg, M.; Becer, C. R. *Green Chem.* **2016,** *18*, 3272-3277.
2 Passerini, M. *Gazz. Chim. Ital.* **1923,** *53*, 331-332. Hanusch-Kompa, C.; Ugi, I. *Tetrahedron Lett.* **1998,** *39*, 2725-2728. Harriman, G. C. B. *Tetrahedron Lett.* **1997,** *38*, 5591-5594. Hulme, C.; Ma, L.; Cherrier, M. P.; Romano, J. J.; Morton, G.; Duquenne, C.; Salvino, J.; Labaudiniere, R. *Tetrahedron Lett.* **2000,** *41*, 1883-1887. Wang, W.; Herdtweck, E.; Domling, A. *Chem. Commun.* **2010,** *46*, 770-772.
3 Banfi, L.; Riva, R.; Basso, A. *Synlett* **2010**, 23-41.

Ugi-Based Assembly of Peripheral Selective Rimonabant Analogues

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Rimonabant is a CB_1 inverse agonist approved in 2006 for the treatment of obesity that was removed from the market in 2008 due to serious psychiatric side effects.[1] Growing evidences confirmed Rimonabant´s neuropsychiatric liabilities are consequence of its binding to central CB_1 receptors, but also that peripheral CB_1 receptor blockade produces similar appetite suppression and weight loss.[2] Accordingly, the search for novel peripheral selective CB_1 ligands have emerged as a promising approach for obesity control.[3] In the frame of a project aimed to identify new lead compounds by using MCR-based approaches, we herein document the discovery and optimization of novel series of brain non-penetrant Rimonabant analogues. The new ligands, that were assembled by Ugi or Ugi-split reactions, exhibit high polar surface area and low Log P while retain excellent CB_1 affinity and selectivity profile.

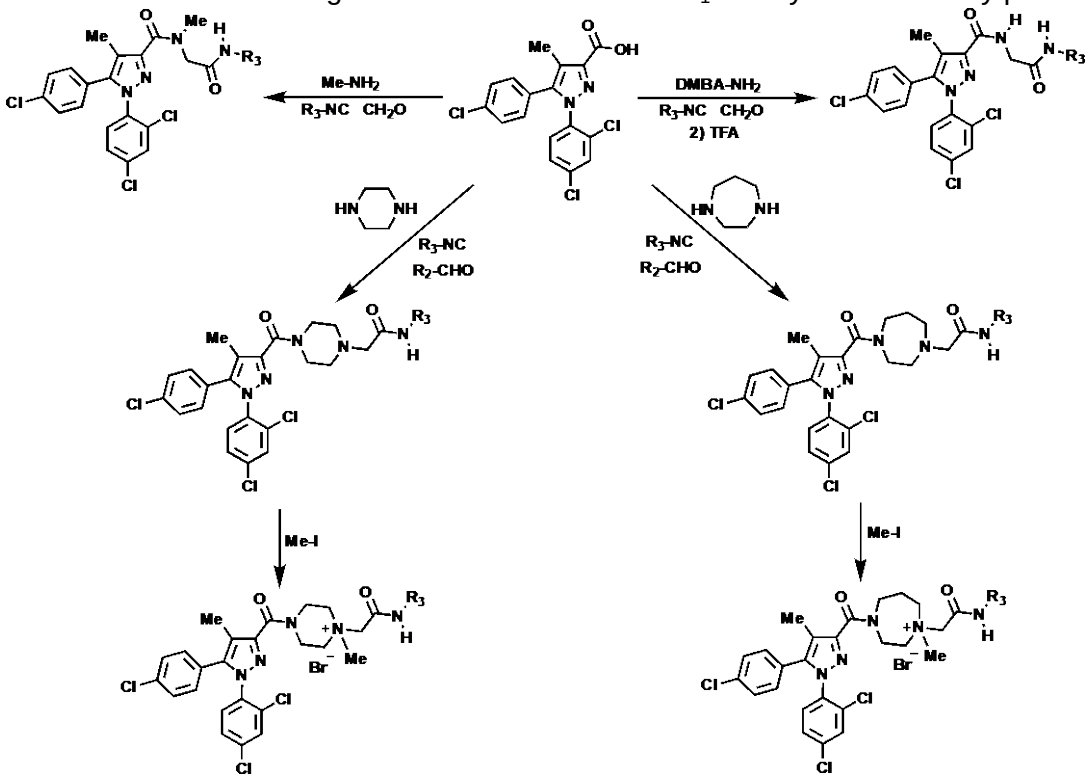

Figure 1. Synthetic scheme employed for the preparation of targeted compounds.

References:

1 Lee, H.K., Choi, E.B., Pak, C.S., *Curr. Top. Med. Chem.,* **2009**, *9*, 482.

2 Tam, J., Vemuri, V.K., Liu, J., Batkai, S., Mukhopadhyay, B., Godlewski, G., Osei-Hyaman, D., Ohnuma, S., Pickel, J., Kunos, G., *J. Clin. Invest*. **2010**, *120*, 3735.
d. Chem. Lett. **2013**, *4*, 1031.

3 Flup, A., Bortoff, K., Seltzman, H., Zhang, Y., Mathews, J., Snyder, R., Fennell, T., Maitra, R., *J. Med. Chem*., **2012**, *55*, 2820.

Peptide macrocyclization assisted by traceless turn inducers derived from Ugi peptide ligation

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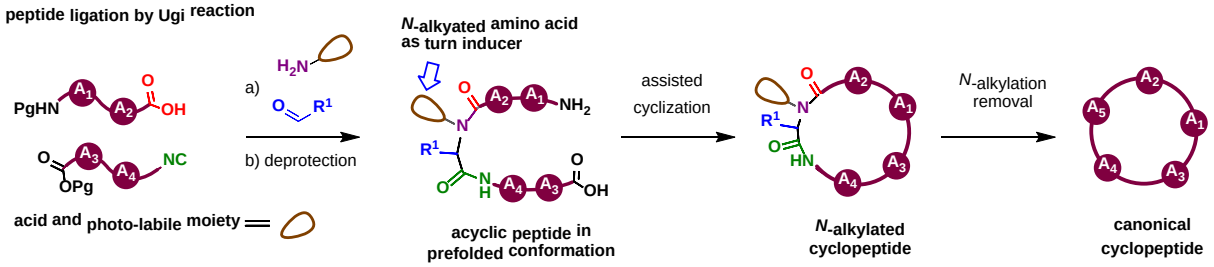
The head-to-tail cyclization of small linear peptides remains one of the most relevant but also often difficult procedures in synthetic chemistry. The main problems of this process are the epimerization of the C-terminal amino acid and the formation of linear and cyclic oligomers.[1] One of the most frequently used strategies is the incorporation of turn-inducing elements, capable of facilitating the macrocyclic ring closure by bringing both termini closer. This research reports a multicomponent approach to the cyclization of small peptides involving the installation of turn-inducing moieties that facilitate the macrocyclization. Our strategy comprises the Ugi ligation of peptide carboxylic acids and isocyanopeptides in the presence of aldehydes and acids or photolabile amines followed by cyclization and cleavage of the backbone *N*-substituents to produce canonical cyclopeptides.[2]



References:

1 White, C. J.; Yudin, A. K. *Nat. Chem*. **2011**, 3, 509.
2 A. R. Puentes, M. C. Morejón, D. G. Rivera, L. A. Wessjohann, *Org. Lett.* **2017**, 19 (15), 4022–4025.

Design and synthesis of selective HDAC6 inhibitors via the Ugi-azide 4CR

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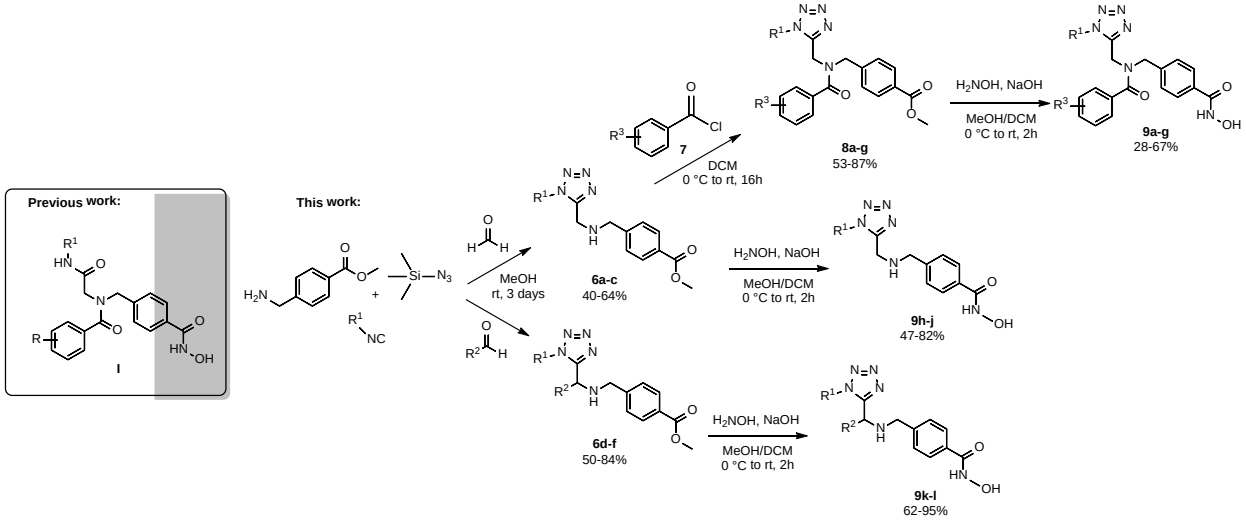
Among the eleven zinc-dependent human histone deacetylases (HDACs), the class IIb isoform HDAC6 has gained particular interest with regards to drug development. Due to its unique substrate spectrum comprising several non-histone proteins such as *α*-tubulin and Hsp90, it is associated with several diseases, e.g. autoimmune disorders and neuro-degenerative disorders, and was also found to be overexpressed in numerous tumour types.[1] Unlike other cancer-related isoforms, however, it is assumed that inhibition of HDAC6 does not induce severe side effects. Consequently, HDAC6 has been identified as a promising drug target.[2]

Despite the highly conserved structure of all HDACs, the first crystal structure of human HDAC6 recently revealed distinct features,[3] which allow the design of isoform-selective inhibitors and clinical trials of first prototypes are currently ongoing. Following previous works on α-peptoid scaffolds as selective HDAC6 inhibitors,[4] we herein report the design, diversification and synthesis of tetrazole-substituted inhibitors.

The library synthesis was performed via the highly versatile Ugi-azide 4-component reaction using a range of isocyanides and aldehydes, 4-methylaminobenzoate and trimethylsilyl azide and yielded the core scaffolds of all final compounds within one step (**6a-f**, 40-84%). Further diversification of some derivatives was achieved by acylation (**8a-g**, 53-87%) using commercially available or *in situ*-generated acyl chlorides **7**. Final aqueous hydroxyl-aminolysis of all precursors gave the desired hydroxamic acids **9a-l** in 28-95% yields. All synthesized hydroxamic acids were evaluated in regards to their HDAC6 selectivity profile. Their inhibitory activity against HDAC1 and HDAC6 was determined in a biochemical assay using recombinant HDAC isoforms and ZMAL (Z-(Ac)Lys-AMC) as substrate. Strikingly, all compounds showed potent inhibitory activity against HDAC6 and at least 10-fold selectivity over HDAC1.



References:

1 J. H. Kalin, J. A. Bergman, *J. Med. Chem*. **2013**, *56*, 6297−6313.
2 O. Witt, H. E. Deubzer, T. Milde, I. Oehme, *Cancer Lett.* **2009**, *277*, 8−21.
3 Y. Hai, D. W. Christianson, *Nat. Chem. Biol.* **2016**, *12*, 741−747.
4 D. Diedrich, A. Hamacher, C. G. W. Gertzen, L. A. Alves Avelar, G. J. Reiss, T. Kurz, H. Gohlke, M. U. Kassack, F. K. Hansen*, Chem. Commun*. **2016,** *52*, 3219−3222.

Synthesis of substituted tetrahydrocarbolines based on enaminone one-pot synthesis

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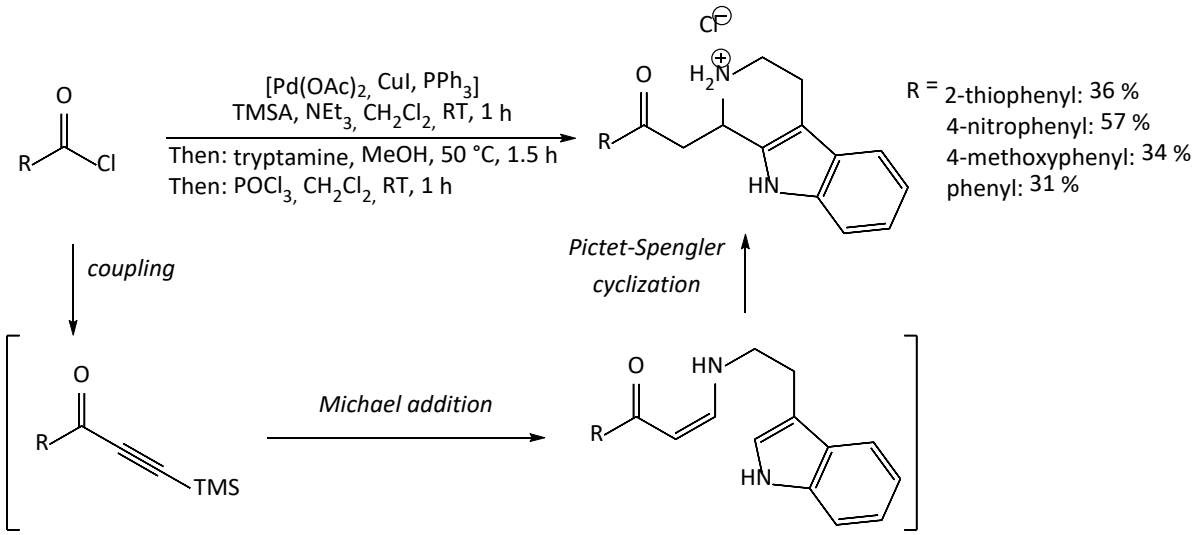
Some 1,2,3,4-tetrahydro-b-carbolines (tryptolines) show significant biological and pharmaceutical activity, which is why their synthesis is still considered to be important.[1][2] A powerful tool for their synthesis is the Pictet-Spengler reaction, where a tryptamine and an aldehyde component are reacted.[2]

Herein we present an alternative route for the synthesis of tryptolines via one-pot four-component reaction based on an already established method for the synthesis of enaminones.[3]



References:

[1] H. Rommelspacher, H. Kauffmann, C. Heyck Cohnitz, H. Coper, *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1977**, *298*, 83-91.
[2] J. Stöckigt, A. P. Antonchick, F. Wu, H. Waldmann, *Angew. Chem. Int. Ed.* **2011**, *50*, 8538-8564.
[3] A. S. Karpov, T. J. J. Müller, *Synthesis* **2003**, 2815-2826.

Gewald reaction for the synthesis of new thiophene[3,2-d]pyrimidine derivatives as potential PPI targeting peptidomimetics

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The Gewald MCR[1] was here applied to synthesize a library of new peptidomimetics, able to mimic different peptidic secondary structures. As a representative case, we selected the p53 protein, a well-defined α-helix structure, very promising target in anticancer therapy. MDM2 and MDMX are proteins with a deep hydrophobic pocket on which the p53 binds; three p53 residues are mainly involved in this interaction: Phe19, Trp23 and Leu26.[2] The average size of the binding pocket is suitable for the design of small molecules which could block the p53/MDM2/MDMX interactions, a type of protein-protein interactions (PPIs) involved in cellular growth and oncogenesis. Among the lead active compounds discovered, one of the most promising interaction disruptors is Nutlin-3a (Figure 1).[3]
Starting from this, since the thiophenic and thienopirimidinic rings are imidazoline bioisosteres, and basing on SAR and docking studies, aiming at a central rigid and planar scaffold, several substituents have been chosen in order to mimic the three principal amino acid side chains of the p53 binding pocket. Two different scaffolds libraries were therefore developed and subsequently submitted to biological tests.

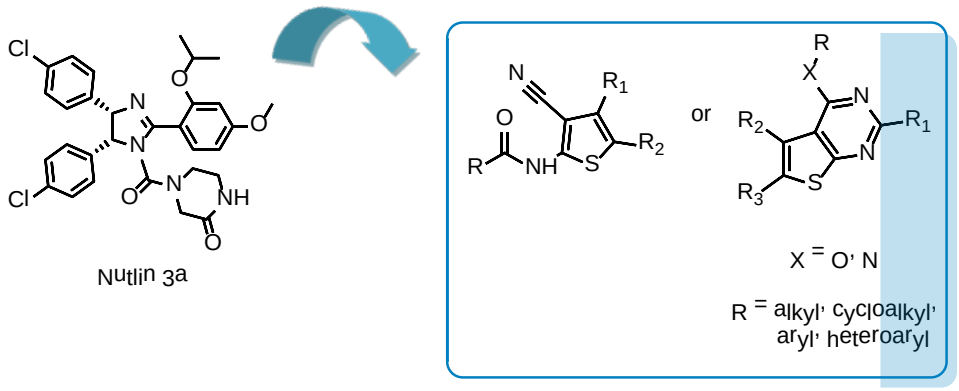

Figure 1. Nutlin-3a and general structures of the designed thiophenic PPI inhibitors.

References:

1 Y. Huang, A. Dömling, *Springer Science, The Gewald Multicomponent Reaction* **2011**, *15*, 3-33.
2 E. Danelius, M. Pettersson, M. Bred, J. Min, M.B. Waddell, R.K. Guy, M. Grøtli, M. Erdelyi, *Org. Biomol. Chem*. **2016**, *14*, 10386-10393.
4 N. Estrada-Ortiz, C.G. Neochoritis, A. Dömling, *ChemMedChem* **2016**, *11*, 757-772.

An Efficient Synthesis of Spiro-oxindole Derivatives by Four-Component Reactions in Solvent-free Condition

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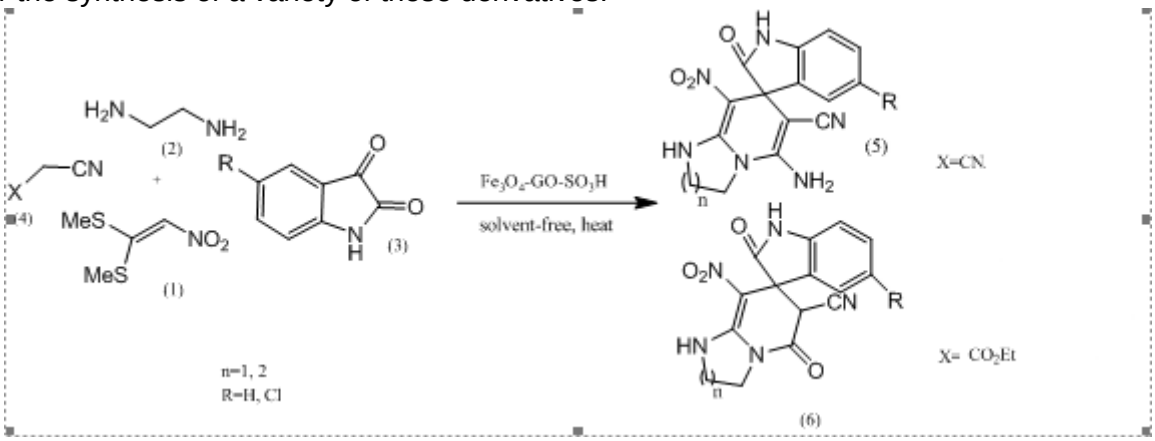
Abstract:

Pyridine derivatives are an important class of aza heterocyclic compounds which are present as skeletal moieties of many natural products and biologically active compounds such as NAD nucleotides, pyridoxol (vitamin B_6), and pyridine alkaloids. Due to the wide application of pyridine derivatives, their synthesis has attracted much attention, and several protocols have been reported in the literature.[1]

These types of compounds have been prepared by different methods[2]. Due to the wide range of pharmaceutical and biological properties of spirooxindole derivatives containing 1,4-dihydropyridine-fused-1,3-diazaheterocycle fragments and in countinuation of our efforts in the synthesis of heterocyclic compounds, herein we report an efficient method for the synthesis of spirooxindolo-tetrahydro imidazopyridines and pentahydro pyridopyrimidines in excellent yields by a four-component reaction of 1,1-bis(methylthio)-2-nitroethene (1), 1,n-diamine (2), isatins (3) and malononitrile derivatives using magnetic acidic graphene oxide as catalyst (Scheme1). Short reaction times, high yields of the products, easy work-up and reusability of the catalyst make this methodology very attractive for the synthesis of a variety of these derivatives.



Scheme1

References:

1) A. Z. Halimehjani, I. N. Namboothiri, S. E. Hooshmand, RSC Adv., 2014, 4(93), 51794.

[a] Alizadeh, A.; Firuzyar, T.; Mikaeili, A. *Synthesis*, **2010**, 3913; [b] Alizadeh, A.; Moafi, L. *Helv. Chim. Acta* **2015**, *98*, 546.

Synthesis and Functionalization of Nitrogen Heterocycles by *Heck*-based Multicomponent Sequence Reaktions

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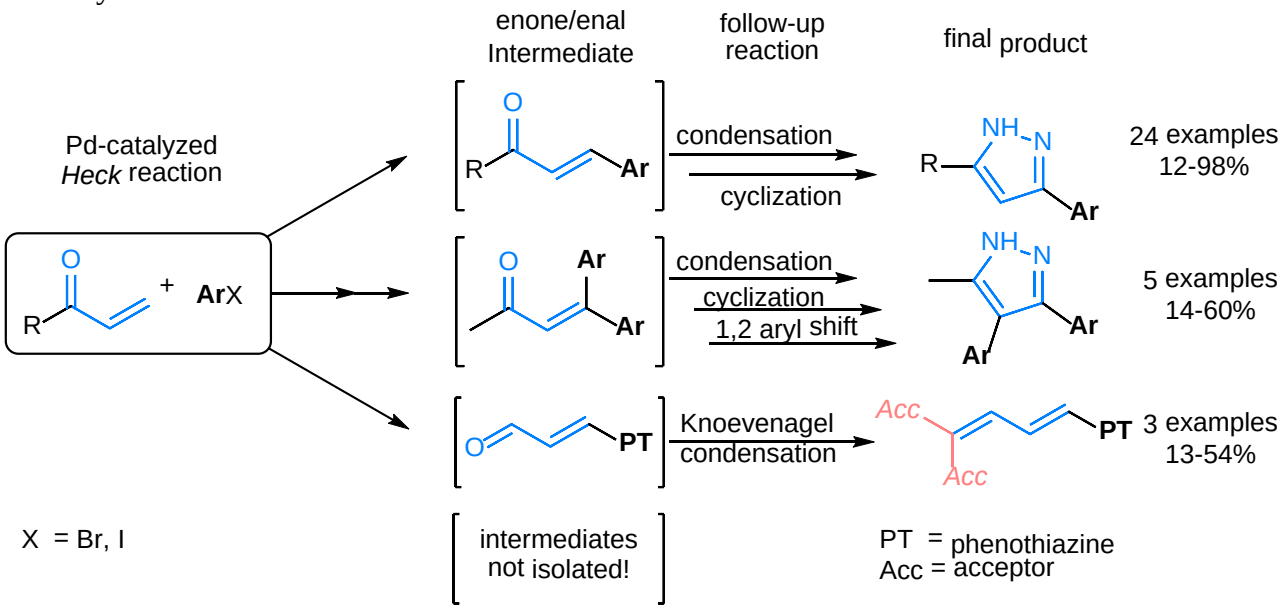
Established already in the early days of organic chemistry,[1] the concept of multicomponent reactions (MCR) has changed the paradigm that only two component reactions could be reliably conducted. Consequently, MCR have become a general reactivity-based principle and synthetic concept.[2] Following this fundamental principle, our group has recently identified a novel catalytic system for the synthesis of *E*-configured *α,β*-unsaturated carbonyl derivatives by exploiting microwave assisted one-pot Pd-catalyzed *Heck* reactions.[3] By the choice of the ligand aryl bromides can be transformed rapidly and under mild reaction conditions. Thereby cinnamaldehyde and chalcone derivatives are obtained in high yields, or they can subsequently undergo cyclocondensations to form pyrazoles in a one-pot fashion. Upon concatenating a subsequent *Knoevenagel* condensation merocyanine-type chromophores can be easily accessed.



While pyrazoles are known for biological and pharmacological activity,[4] phenothiazine based merocynine chromophores have successfully been applied in dye-sensitized solar cells (DSSCs). By expanding π-system, the bathochromic shift can be adjusted to reach the maximum efficiency of DSSC.[5],[6]

[1] A. Strecke, *Justus Liebigs Ann. Chem.* **1850**, *75*, 27–45. [2] T. J. J. Müller, *Science of Synthesis Series*, Georg Thieme Verlag KG, Stuttgart **2014**, 5–27. [3] J. Panther, M. Stephan, F. Wilbert, P. Ozog, T. J. J. Müller, manuscript in preparation. [4] A. Schmidt, A. Dreger, *Curr. Org. Chem.* **2011**, 15, 1423-1463. [5] T. Meyer, D. Ogermann, A. Pankrath, K. Kleinermanns, T. J. J. Müller, *J. Org. Chem.* **2012**, *77*, 3704-3715. [6] A. M. Grabarz, A. D. Laurent, B. Jędrzejewska, A. Zakrzewska, D. Jacquemin, B. Ośmiałowski, *J. Org. Chem.***2016**, *81*, 2280-2292.

Isocyanide Based Multicomponent Reaction of Diamines: Further Expansions, Modifications, and Applications for Focused Libraries Design and Synthesis

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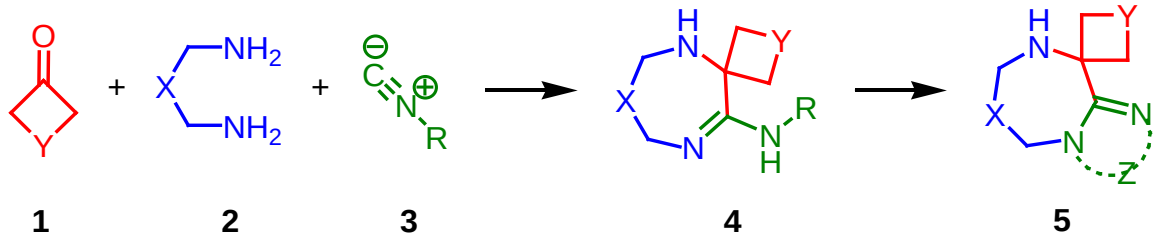
Well-defined spatial orientation and conformational rigidity of spiro-heterocycles are of significant interest to the structure-based drug discovery. Focused compound libraries based on these systems are useful in a fragment-based screening, studies of protein-protein interaction and allosteric modulation. In addition, properly populated compound sets based on spiro heterocycles consistently feature lead-like physico-chemical properties including solubility and biomembrane permeability. Although numerous approaches to these systems have been described, they are relatively specific and only result in a limited number of compounds per template. For instance, cyclic ketones in multicomponent reactions are often used as reagents, which bearing spiro fragments into the target molecules. Their use in reactions involving bifunctional reagents already made it possible to obtain carboxamide- or tetrazole-substituted spirocyclic *γ*-lactams.[1] In order to device a general strategy to access polycyclic spiro-cycles, we have elaborated an isocyanide-based multicomponent condensation shown below:



1 **2** **3** **4** **5**

The key step of our strategy is a three-component reaction of (hetero)cyclic ketones **1**, 1,2- or 1,3-diamines **2**, and isocyanides **3** to yield the targeted heterocylic core **4**. Previously, the isocyanide-based multicomponent reaction involving 1,2-diamines leading to piperazine-2-imines was investigated. Then this isocyanide-based multicomponent reaction was broadened to the synthesis of 1,4-diazepine-2-amines if 1,3-diamines were involved as starting diamines. The IMCR was expanded further to include a wide range of (hetero)cyclic ketones and aliphatic or (hetero)aromatic diamines resulting in diverse spiro-heterocyclic scaffolds.[2] Amidine moiety in **4** can be further converted into the respective 1,3-diazaheterocyclo-annulated tricyclic spiro-compounds **5**. Scope, limitations, and utility of this reaction to the synthesis of a diverse library will be disclosed.

References:

1 V. Stolyarenko, A. Evdokimov, *Mendeleev Commun.* **2013**, *23*, 108, 233.
2 V. Kysil, A. Khvat, *Eur. J. Org.Chem.* **2010**, 1525.

Smart ROS-probes by Ugi-4CR

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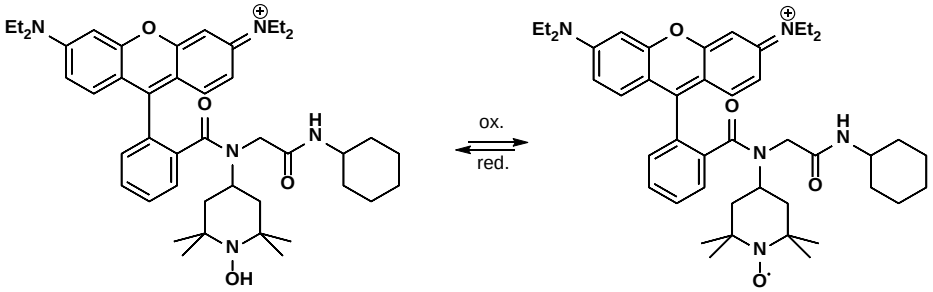
The monitoring of biological processes within cells is an ongoing challenge, therefore, chemical probes have been generated to determine and analyze them. Among the cellular processes which disclose a clear indication of the nature and the status of a cell is the formation of active radical oxygen species (ROS, e. g. hydroxy radicals) *in vivo*. Its generation in excess causes cellular damage and is considered to aid in initiating radical chain reactions, which may lead to oxidative stress. Here we want to present our results on the synthesis of smart ROS-probes by Ugi-multi-component-reactions, which allows for a fast, reliable and highly diverse generation of rhodamine-TEMPO-adducts.[1] The EPR- and fluorescence data upon oxidation/reduction will be discussed.



fluorescent non-fluorescent

References:

1 S. Brauch, M. Henze. B. Osswald, K. Naumann, L. A. Wessjohann; van Berkel, S. S.; B. Westermann, *Org. Biomol. Chem*. **2012**, *10*, 958–965.

Exploring Multi-Component Reactions to Synthesize Covalent Inhibitors

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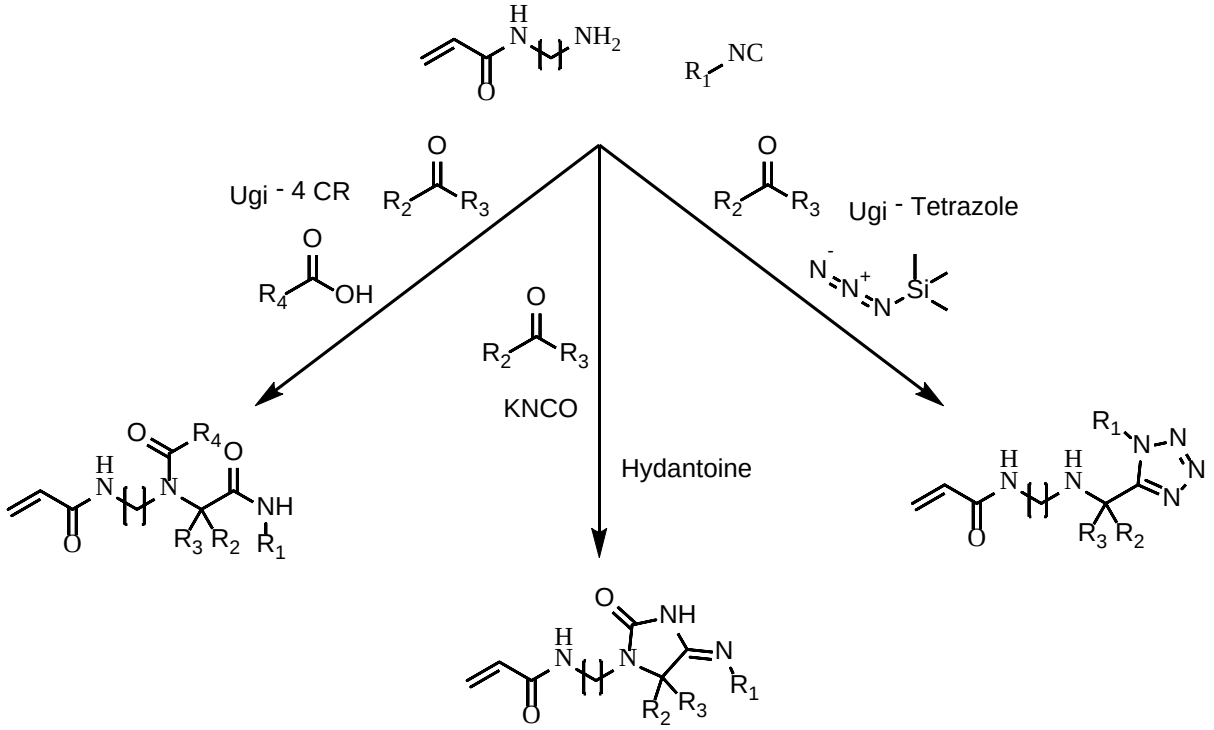
Covalent inhibitors play important role in drug discovery and therapeutics. About 30% of marketed drugs are covalent inhibitors, ranging from obesity to cancer.[1] The toxicity of covalent inhibitors is a major concern, but the advantages provided by them offer a large opportunity of exploring them even further. There are different warheads that act as covalent inhibitors, for example α,β-unsaturated carbonyl, epoxide, β-lactam, β-lactone, halomethyl, α-keto derivatives, etc.[2] Multi-component reactions are a powerful tool that can be used to synthesize covalent inhibitors. This work focused on synthesizing α,β-unsaturated carbonyl using multi-component reactions, a Michael acceptor that binds covalently towards cysteine.



References:

1 A. R. Bauer, *Drug Discov. Today.* **2015**, *20*, 1061-1073.
2 S. D. Cesco, J. Kurian, C. Dufresne, A.K. Mittermaier, N. Moitessier, *Eur. J. Med. Chem.* **2017**, *138*, 96-114.

Zn(L-proline)$_2$ as an Efficient and Reusable Catalyst for Multicomponent Synthesis of Heterocyclic Compounds

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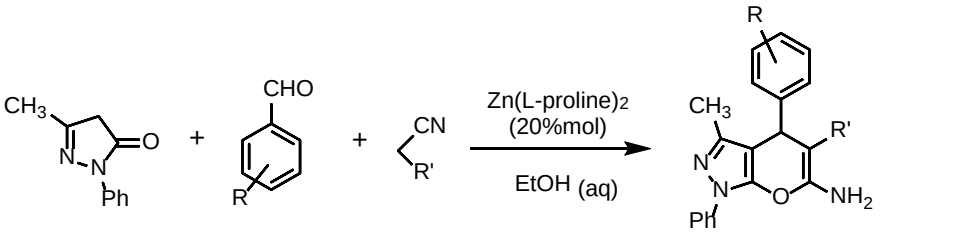
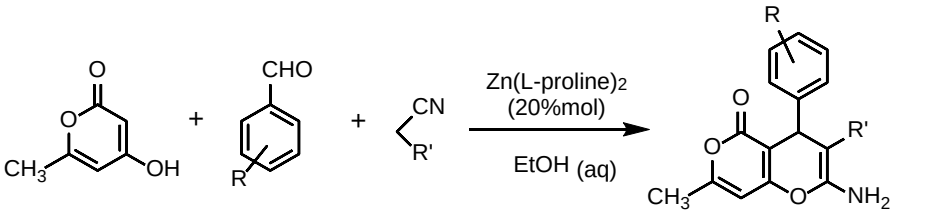
Proline is the most prominent amino acid for the coordination with Zn. The secondary amine and the carboxylate functional groups are ideally suited for complexation with Zn^{2+} in low coordination number, which makes Zn complex a moderately soft Lewis acid. Recently Zn(L-proline)$_2$ complex has emerged as a powerful catalyst for various transformations such as aldol and nitroaldol condensation,[1] Hantzsch condensation,[2] and some other reactions including heterocyclic synthesis.[3] The Zn(L-proline)$_2$ complex is not dissociated under different reaction conditions. The complex is soluble in water which makes the reaction conditions milder and safer. The solubility nature of the catalyst can facilitate the separation of the products from the catalyst and the used catalyst can be recycled and used for the next reaction.

We have utilized Zn(L-proline)$_2$ complex as a catalyst in several tandem Knoevenagel-Michael Cyclocondensation reactions between aromatic aldehydes and malononitrile or ethylcyanoacetate and active CH acids such as 1,3-dicarbonyl compounds to form various heterocyclic systems.



Dihydropyrano[2,3-*c*]pyrazoles



Dihydropyrano[4.3-*b*]pyranes

Several aspects of Zn(L-proline)$_2$ catalysts in similar reactions will be presented.

References:

1 V.R. Sivamuragan, S. Kumar, M. Palanichamy, V. Murugesan, *J. Heterocycl. Chem.* **2005**, *42*, 969.
2 V.R. Sivamurugan, A. Vinu, M. Palanichamy, V. Murugesan, *Heteroat. Chem.* **2006**, *17*, 267.
3 M. Kidawi, A. Jain, *Appl. Organometal. Chem.*, **2012**, *26*, 528.

Application of Multicomponent Reactions (MCRs) for The Synthesis of Natural products and Biologically Important Scaffolds

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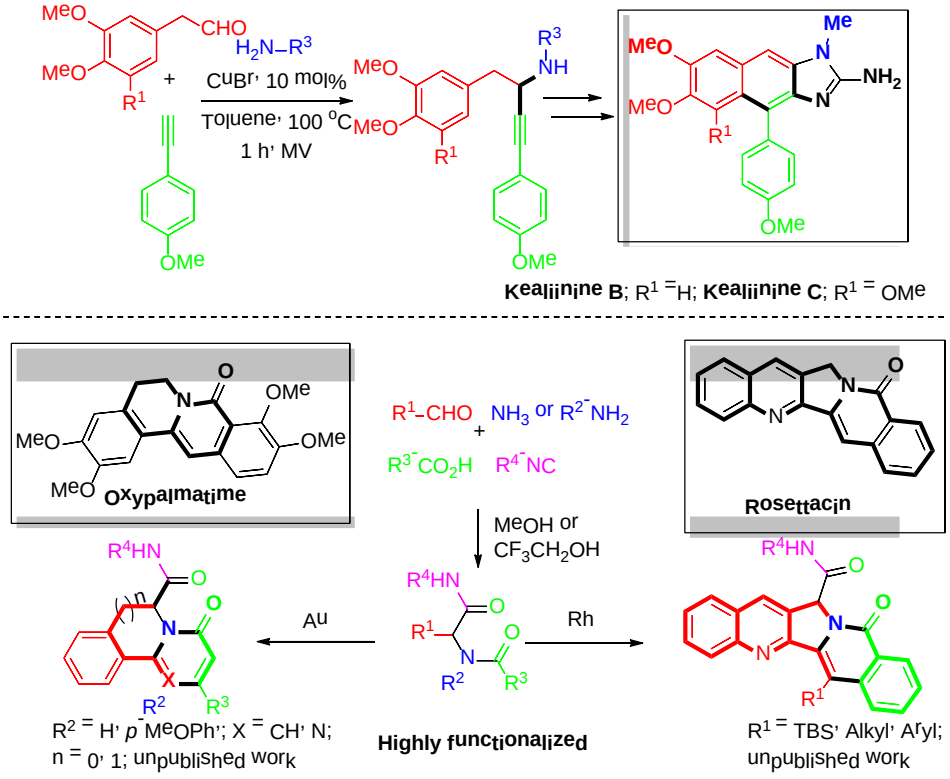
Natural products as the inspiration and the starting point of novel drugs have attracted many medicinal chemists attention. And molecules with the same key scaffold have potential similar biological or physicochemical activity. Multicomponent Reactions (MCRs) are very powerful tool for library synthesis aimed at carrying out structure–activity relationship (SAR) studies of scaffolds exist in bio-important molecules, which are an essential part of the research performed in pharmaceutical and agrochemical companies.
We utilized MCRs (A3 coupling and Ugi reaction) for synthesis of the intermediates. Sequence transformations of these intermediates were successfully utilized for the synthesis of **Kealiinines** alkaloids[1] as well as the key scaffolds exist in **Rosettacin** and **Oxypalmatime**.



References:

1 G. Tian, P. Fedoseev, E. V. Van der Eycken, *Chem. Eur. J.* **2017**, *23*, 5224 – 5227

Palladium/NHC-catalyzed intramolecular cyclization to synthesis *N*-phenyl-1*H*-indazole-1-carbothioamide as a novel class of indazole derivatives

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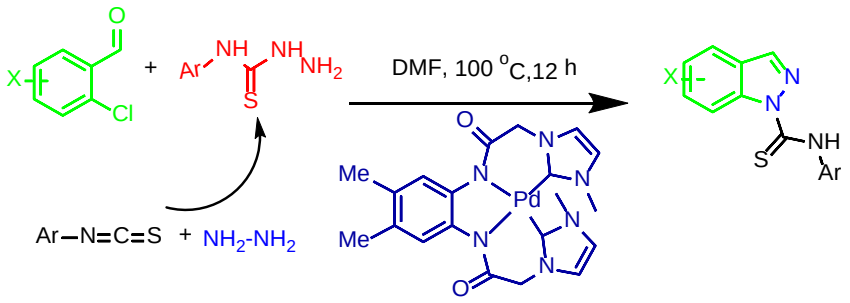
Multicomponent reactions have been known as a powerful method to prepare a wide range of organic compounds for over 150 years. In addition, the synthesis of heterocycle cores by synthetically simple and convenient method is one of the most important goals of modern organic synthesis.[1] Regarding to these two aspects, we get interested in combinatorial chemistry. There are some methods for the construction of a wide range of heterocyclic systems. Investigation of biologically active heterocyclic compounds containing the indazole core has resulted in the exploration of potent HIV protease inhibitors, serotonin receptor antagonists, aldol reductase inhibitors, and acetylcholinesterase inhibitors.[2a-c] On this subject, our research group report a useful three-component reaction for the synthesis of *N*-aryl-1*H*-indazole-1-carboxamide. In order to achieve these kinds of heterocyclic compounds, we use Palladium/NHC as an efficient catalyst for intramolecular coupling. The structures of the products were characterized by NMR and Mass spectroscopy and elemental analysis.



References:

1 J. D. Sunderhaus, S. F. Martin, *Chem. Eur. J.* **2009**, 15, 1300.
2 S. Tomassi, J. Lategahn, J. Engel, M. Keul, H. L. Tumbrink, J. Ketzer, T. Mühlenberg, M. Baumann, C. Schultz-Fademrecht, S. Bauer, D. Rauh, *J. Med. Chem*. **2017**, 60, 2361 ; (b) X. Xiong, Y. Jiang, D. Ma, *Org. Lett*. **2012**, 14, 2552; (c) Y. Lian, R. G. Bergman, L. D. Lavis, J. A. Ellman, *J. Am. Chem. Soc*. **2013**, 135, 7122.

Enantioselective Vinylogous Michael-type Addition of *α*-Angelica Lactone to Electrophilic 2-Iminochromenes

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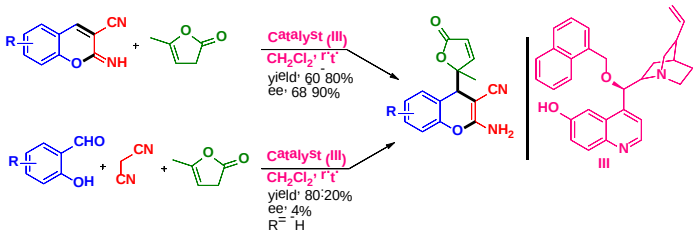
Heterocyclic compounds are the important class of organic compounds which exhibits potent biological activities.[1] Chromene heterocyclic skeletons are widely distributed in natural products and they have been explored for their medicinal properties.[2] The 2-amino-4*H*-chromene moiety is a well known heterocyclic core found in protein kinase inhibitor (MK-2)[3], tumor antagonist HA14-1[4] and anticancer drug MX58151[5]. Inspiring from the biological importance of 2-amino-4*H*-chromenes, we plan to construct these chiral core structures with increased functionality.

Herein, we disclose the enantioselective synthesis of 2-Amino-4-(2-Furanone)-4*H*-chromene-3-carbonitrile by vinylogous Michael-type addition of *α*-angelica lactone to electrophilic 2-iminochromenes in the presence of cinchonine alkaloid-based organocatalyst. The optimized conditions were then used to explore the generality of the reaction. Various substituents on the iminochromene ring were explored, in case of electron withdrawing groups we have achieved excellent diastereo- and enantioselectivity. The present methodology is found to be very efficient and also provides a facile access to produce chiral 2-furanone containing heterocyclic chromenes in one step.



We also explored one-pot three-component reactions under our optimized conditions resulted in desired chiral 2-Amino-4-(2-Furanone)-4*H*-chromene-3-carbonitriles with high diastereoselectivity and poor enantioselectivity.

References:

1. J. B. Harborne, The Flavanoids−Advances in Research; Chapman & Hall: London, **1988**; B. A. Bohm, J. B. Choy, A. Y.-M. Lee, *Phytochemistry* **1989**, *28*, 501.
2. S. G. Das, J. M. Doshi, D. Tian, S. N. Addo, B. Srinivasan, D. L. Hermanson, C. Xing, *J. Med. Chem.* **2009**, *52*, 5937.
3. D. R. Anderson, S. Hegde, E. Reinhard, L. Gomez, W. F. Vernier, L. Lee, S. Liu, A. Sambandam, P. A. Snider, L. Masih, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1587.
4. J. L. Wang, D. Liu, Z. Zhang, S. Shan, X. Han, S. M. Srinvasula, C. M. Croce, E. S. Alnemeri, Z. Huang, *Proc. Natl. Acad. Sci.* **2000**, *97*, 7124.
5. P. Vachal, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 10012; T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672.

With unprotected amino acids to tetrazolopeptidomimetics

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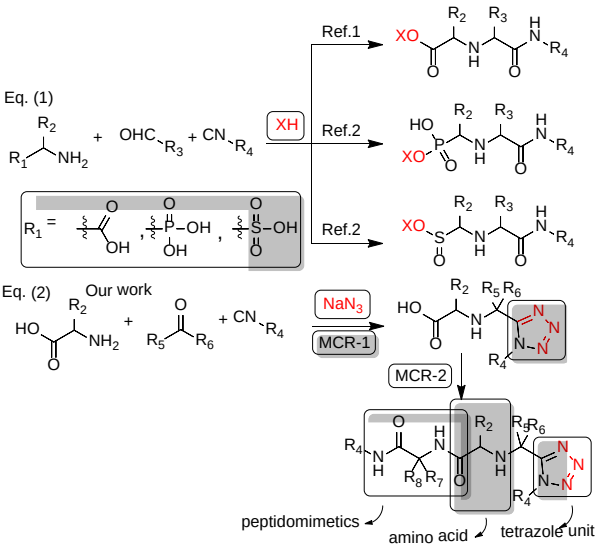
Very effective variations of the Ugi-reaction were reported by using amino acids as one of the starting components. Our group has reported a ‘‘truly’’ fourcomponent reaction for the synthesis of iminodicarboxamides by employing amino acids directly in an U-5C-4CR.[1] In 2013, Lammerhofer et al. reported the synthesis of phosphopeptidomimetics by utilizing aminophosphonic acids in U-5C-4CR.[2]Even though unprotected amino acids and aminophosphonic acids are utilized in various Ugi-type reactions, to the best of our knowledge, this is the first study on the use of unprotected amino acids in the Ugi-tetrazole reaction.[3]

Here we describe the direct usage of C,N-unprotected amino acids in Ugi-tetrazole reactions to produce a novel class of acid-tetrazole compounds. Surprisingly, only the tetrazole Ugi product is found and not traces of other possible Ugi type reactions. Based on this reaction pathway we have designed the synthesis of novel tetrazole-peptidomimetics. A high level of structural diversity can be achieved using this isocyanide based multicomponent reaction(IMCR), providing a platform for the production of functionalized building blocks for novel bioactive molecules and nontraditional scaffolds which previously were not accessible.



References:

(1) Khoury, K.; Sinha, M. K.; Nagashima, T.; Herdtweck, E.; Domling, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 10280.
(2) Gargano, A. F. G.; Buchinger, S.; Kohout, M.; Lindner, W.; Lammerhofer, M. *J. Org. Chem.* **2013**, *78*, 10077.
(3) Madhavachary, R.; Wang, Q.; Domling, A. *Chem. Commun.* **2017**, *53,* 8549.

Acoustic Dispensing-Enabled Isoquinoline Scouting

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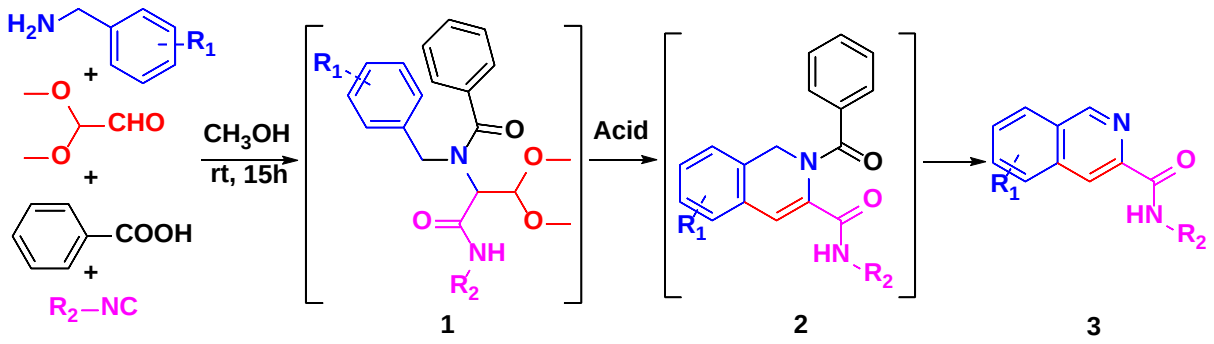
We designed a one-pot isoquinoline synthesis based on a Ugi-4CR of electron rich benzyl or heterocyclic benzylamines, isocyanides, 2,2-dimethoxyacetaldehyde, and an acid followed by an acid catalyzed cyclisation.[1,2] To test the idea, we synthesized a random library of 384 derivatives based on 10 (hetero)benzylamines and 69 different isocyanides on a nM scale using nL scale acoustic dispensing technology in a one compound per well fashion. The great majority of reactions went surprisingly well according to SFC-MS quality control. We then resynthesized and fully characterized 30 random examples of highly substituted isoquinolines on a multi-mg scale in medium to excellent yields. Also, a multi gram scale-up was performed. The herein described acoustic dispensing-enabled reaction scouting resulted in a novel highly versatile isoquinoline synthesis with great scope. It is showing a pipeline from fast and efficient nL scale scouting to mg to gram scale synthesis in the discovery of a preparative useful novel reaction.



References:

1. (a) Birch, A. J.; Jackson, A. H.; Shannon, P. V. *J. Chem. Soc.*, Perkin Transactions 1, **1974**, 2185. (b) Birch, A. J.; Jackson, A. H.; Shannon, P. V. *J. Chem. Soc.*, Perkin Transactions 1, **1974**, 2190. (c) Gensler, W.; Lawless, S.; Bluhm, A.; Dertouzos, H. *J. Org. Chem.* **1975**, *40*, 733. (d) Hendrickson, J. B.; Rodriguez, C. *J. Org. Chem.* **1983**, *48*, 3344.
2. (a) Głuszyńska, A.; Rozwadowska, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 2359. (b) Boudou, M.; Enders, D. *J. Org. Chem.* **2005**, *70*, 9486. (c) Kościołowicz, A.; Rozwadowska, M. D. *Tetrahedron: Asymmetry* **2006**, *17*, 1444. (d) Chrzanowska, M.; Grajewska, A.; Meissner, Z.; Rozwadowska, M.; Wiatrowska, I. *Tetrahedron* **2012**, *68*, 3092. (e) Li, B.; Wang, G.; Yang, M.; Xu, Z.; Zeng, B.; Wang, H.; Zhu, W. *E. J. Med. Chem.* **2013**, *70*, 677. (f) Naciuk, F. F.; Milan, J. C.; Andreão, A.; Miranda, P. C. *J. Org. Chem.* **2013**, *78*, 5026. (g) Banerjee, S.; Zare, R. N. Angew. Chem. Int. Ed. 2015, 54, 14795. (h) Vázquez-Vera, Ó.; Sánchez-Badillo, J. S.; Islas-Jácome, A.; Rentería-Gómez, M. A.; Pharande, S. G.; Cortes-García, C. J.; González-Zamora, E. *Org. Biomol. Chem.* **2017**, *15*, 2363.

Solubility Tuning and Photophysical Properties of Fluorescent Cation- and Proton-Sensitive 2,4-Diarylpyrano[2,3-*b*]indoles

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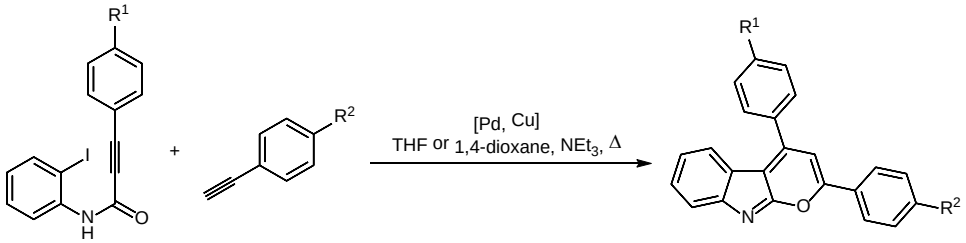
Functional chromophores are widely applied and are used for instance in dye-sensitized organic solar cells,[1] light-emitting diodes[2] or as chemosensors.[3] For the latter, an embedded switching element like a basic nitrogen atom or phenolic hydroxyl group is needed. Upon binding to an analyte, the chemosensor significantly changes its absorption or emission properties.[4]

As shown by our group, 2,4-diarylpyrano[2,3-*b*]indoles **3** can be synthesized via a Pd-Cu-catalyzed insertion-coupling-cycloisomerization domino reaction. Starting from alkynoyl *o*-iodo anilides **1** and terminal arylacetylenes **2** the tricyclic systems are obtained in moderate yields. 2,4-Diarylpyrano[2,3-*b*]indoles **3** are nonfluorescent in solid-state and solution. However, upon complexation with metal ions, protonation or quaternation bright green fluorescence is induced, therefore, they can be potentially applied as chemosensors.[5]

A prerequisite for cation- and proton-sensitive chemosensors is their solubility in a broad polarity spectrum. Here, different 2,4-diarylpyrano[2,3-*b*]indoles **3** have been synthesized. Additionally, branched oligo(ethylene glycol) side chains or long alkyl chains, for increasing the solubility in either organic or aqueous media were introduced. Solubility studies in various solvents and solvent mixtures were performed, ultimately employing the photophysical changes as a readout.



References:

1 A. Mishra, M. K. R. Fischer, P. Bäuerle, *Angew. Chem. Int. Ed.* **2009**, *48*, 2474-2499.
2 J. Shinar, R. Shinar, *J. Phys. D: Appl. Phys*. **2008**, *41*, 133001/1-133001/26.
3 L. Basabe-Desmonts, D. N. Reinhoudt, M. Crego-Calama, *Chem. Soc. Rev.* **2007**, *36*, 993-1017.
4 A. J. Zucchero, J. N. Wilson, U. H. F. Bunz, *J. Am. Chem. Soc.* **2006**, *128*, 11872-11881.
5 J. Schönhaber, W. Frank, T. J. J. Müller, Org. Lett. **2010**, *12*, 4122-4125.

A platform for automated nanomole-scale MCR reaction screening and applied to micromole-scale synthesis

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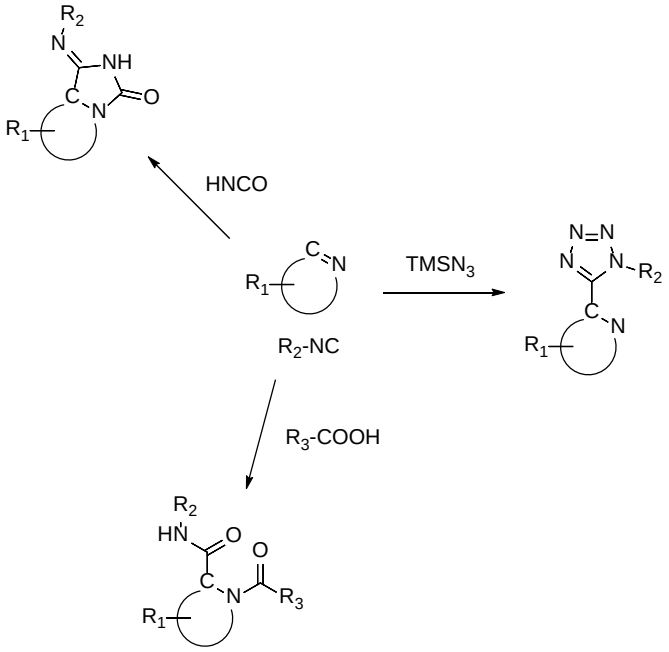
At the forefront of new synthetic endeavors, especially for drug discovery, large amounts of novel compounds are tightly needed. An automated platform enabling high-throughput experimentation for reaction exploring for preparative reaction scale-up would be a transformative advance.[1] We report here the applied of Echo automated synthesis system to study a diverse range of reaction variables in three different types of reaction, Ugi classical, Ugi tetrazole and Hydantoin synthesis respectively. The cyclic Schiff bases were used as starting materials and 387 reactions could be finished in 3 hours. Afterwards, the supercritical fluid chromatography-mass spectrometry datum were generated for 387 reactions within 16 hours. According to the results, more than 50% reactions worked and directly produced good quality of desired agents. The novel products were also replicated in traditional synthesis at the micromole-scale to provide good to excellent yields.



References:

1. (a) Damith Perera, Joseph W. Tucker, *Science*, **2018**, *359*, 429–434; (b) Alexander Buitrago Santanilla, Erik L. Regalado, *Science*, **2015**, *347*, 49-53.

Fragment-based and Multicomponent Synthesis of Polyphenols-Peptide Hybrids and their Evaluation as Amyloid Aggregation Inhibitors

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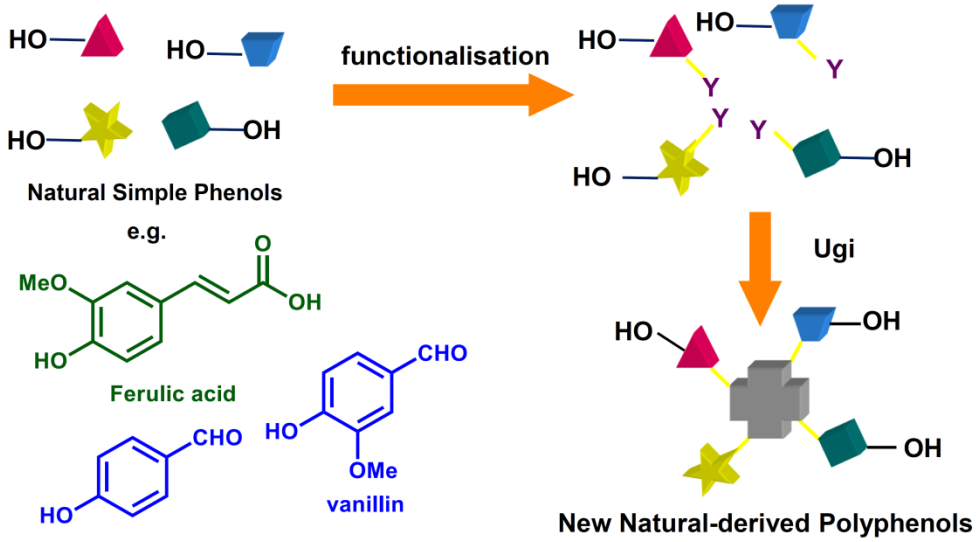
Alzheimer's disease (AD) is an irreversible and progressive neurodegenerative disorder and it is the most common cause of dementia. Although AD it is not clearly understood, it is strictly correlated to the presence in the brain of two types of aggregates: the intracellular neurofibrillary tangles and the extracellular amyloid plaques. The inhibition of amyloid aggregation is thus a promising therapeutic approach for the AD.

Recently, the ability of few natural and simple polyphenols (e.g. epigallocatechin gallate, curcumin) to inhibit the amyloid aggregation has been highlighted.[1] In addition, it is known that this class of compounds is endowed with antioxidant and anti-aging properties. However, their use as drugs is hindered by poor stability under physiological conditions and/or difficult blood-brain barrier permeability.

Aiming at overcoming this limitation, we have designed a very short synthetic sequence, based on the Ugi multicomponent reaction, to access a series of unnatural polyphenol-peptide hybrids. Most fragments used in this approach are bio-based phenols, that have been, in some cases, simply derivatized to afford the functionality needed for the Ugi reaction. Herein, the optimization of the synthetic strategy[2] and the *in vitro* and *in vivo* results of the most active compounds will be discussed.[3]



References and notes:

1 R. Randino, M. Grimaldi, M. Persico, A. De Santis, E. Cini, W. Cabri, A. Riva, G. D'Errico, C. Fattorusso, A. M. D'Ursi, M. Rodriquez, *Sci. Rep.*, **2016**, *6*, 38846.

2 C. Lambruschini, D. Galante, L. Moni, F. Ferraro, G. Gancia, R. Riva, A. Traverso, L. Banfi C. D'Arrigo, *Org. Biomol. Chem.*, **2017**, *15*, 9331.

3 This study was supported by the Fondazione Cariplo under the "Integrated Biotechnology and Bioeconomy" programme.

Donate-like mesoporous graphitic carbon nitride as a robust and heterogeneous organocatalyst for the one-pot synthesis of 2-amino-3-cyanopyridines

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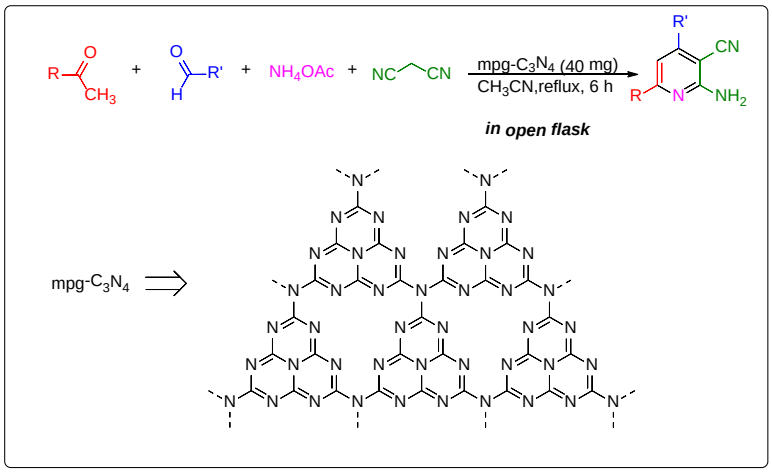
The pyridine substructure as one of the most prevalent heterocycles often play an indispensable role in chemical synthesis and the pharmaceutical industry.[1] Among them, 2-amino-3-cyanopyridines allowed an access to many demonstrated bio-active agents.[2] The prominence of these compounds has led to various methods for synthesizing such compounds in recent years.[3] The most common synthetic approach to these pyridine derivatives is the multicomponent reaction (MCR) of aldehydes, ketones, malononitrile, and ammonium acetate. However, most of these methods often involve the use of expensive reagents or metal-based catalysts. Considering both economic and environmental issues, the best option for catalyst-based synthesize of such compounds is heterogeneous catalysts and mesoporous graphitic carbon nitride (mpg-C_3N_4) can be an attractive candidate for this purpose. The incorporation of nitrogen atoms in the carbon nanostructure can enhance the basicity of this compound. Building on our previous research [3b] now, an efficient procedure for the synthesis of 2-amino-3-cyanopyridines via an mpg-C_3N_4 catalyzed four-component condensation is presented:



References

1 a) Pharmaceutical Chemistry, H. J. Roth, A. Kleemann (Eds.), Drug Synthesis;,Vol. 1, John Wiley & Sons, New York, 1988; b) R. Ghorbani-Vaghei , Z. Toghraei-Semiromi, R. Karimi-Nami, *C. R. Chim.* **2013**, *16*, 1111.

2 A. S. Girgis, A. Kalmouch, H. M. Hosni, *Amino Acids* **2004**, *26*, 139.

3 a) A. Yahyazadeh, E. Abbaspour-Gilandeh, M. Aghaei-Hashjin, *Catal. Lett.* **2018**, *148*, 1254; b) D. Khalili, *Tetrahedron Lett.* **2016**, *57*, 1721.

HFIP as a Novel Acid Component in the Passerini Reaction: One-Pot Access to β-Amino Alcohols

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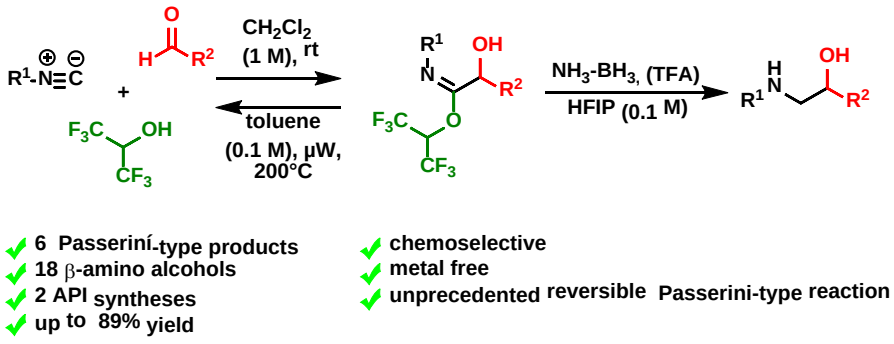
Isocyanide-based multicomponent reactions have received much interest over the past decades. Still, new discoveries continue to be made about these complex reactions. In addition to post-condensation modifications, new developments in this field are based on changing the nature of the traditional reaction pathway, either by single reactant replacement[1,2] or by interrupting the reaction mechanism.[3] Herein we report a new Passerini-type reaction in which HFIP functions as the acid component.[4] The reaction tolerates a broad range of isocyanides and aldehydes, and the resulting imidates can be reduced to medicinally important β-amino alcohols under mild, metal-free conditions. Moreover, the observation that the imidate products undergo an unprecedented retro- Passerini-type reaction under microwave irradiation provides valuable information about the general mechanism of the Passerini reaction and related reactions.



References

[1] Ganem, B. *Acc. Chem. Res.* **2009**, *42*, 463.
[2] Ruijter, E.; Scheffelaar, R.; Orru, R. V. A. *Angew. Chemie Int. Ed.* **2011**, *50*, 6234.
[3] Saya, J. M.; Oppelaar, B.; Cioc, R. C.; van der Heijden, G.; Vande Velde, C. M. L.; Orru, R. V. A.; Ruijter, E. *Chem. Commun.* **2016**, *52*, 12482.
[4] Saya, J. M.; Berabez, R.; Broersen, P.; Schuringa, I.; Kruithof, A.; Orru, R. V. A.; Ruijter, E. *Org. Lett.* **2018**, *20*, 3988.

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